IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff	)	
v.	)	C.A. No. 23-975 (RGA) (SRF)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

PLAINTIFF'S ANSWERING POST-TRIAL BRIEF REGARDING VALIDITY

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

TABLE OF ABBREVIATIONS

’327 patent	U.S. Patent No. 11,826,327
6MWD	6 minute walk distance
Asserted Claims	Claims 1, 5, 6, 9, 14, 17
FDA	Food and Drug Administration
FVC	Forced vital capacity
Group 1	WHO Group 1 PH, pulmonary arterial hypertension
Group 3	WHO Group 3 PH, including PH-ILD and PH-COPD
Lancet Publication or Nathan 2021	PTX-34; Nathan SD, et. al., *Inhaled Treptrostinil and Forced Vital Capacity in Patients with Interstitial Lung Disease and Associated Pulmonary Hypertension: a Post-Hoc Analysis of the INCREASE Study*, Lancet Respir Med. 2021 Jun 29, https://doi.org/10.1016/S2213-2600(21)00165-X
Liquidia	Liquidia Technologies, Inc.
Liquidia’s 505(b)(2) NDA	NDA 213005
New England Journal of Medicine Publication or Waxman 2021	PTX-147; Waxman A, et. al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N Engl J Med. 2021 Jan 28, 384(4):325-334
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	pulmonary arterial hypertension (Group 1)
PH	pulmonary hypertension
PH-ILD	pulmonary hypertension associated with interstitial lung disease
RLD	Reference listed drug
UTC	United Therapeutics Corporation

ASSERTED CLAIMS: '327 PATENT

Claim	Claim Limitation
1[preamble]	A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising
1[a]	administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease
1[b]	an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof
1[c]	in a single administration event that comprises at least 6 micrograms per breath.
5	The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
6	The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
9	The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
11 (*not asserted*)	The method of claim 1, wherein said administering is performed by a pulsed inhalation device.
14	The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.
17	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

I. INTRODUCTION

Liquidia's case is fundamentally flawed. It relies on theories foreclosed by law and others not even preserved, e.g., no patentable weight, prior use. Liquidia's invalidity theories also rely on inferences manufactured through attorney argument that are wholly unsupported by evidence.

1. This case is most directly resolved by straightforward application of § 102(b)(2)(C), which renders the '793 patent not prior art. Thus, Liquidia's *only* basis for invalidity of claim 14 crumbles. And Liquidia stipulated to infringement of claims 1 and 14. The obviousness case also fails across all asserted claims because Liquidia applies impermissible hindsight to conclude that the POSA—with only two-years experience treating PH-ILD—would be motivated to cherry-pick uncontrolled data from different formulations (solution/dry powder) and a spectrum of administrations (nebulizer/intravenous/DPI). Even if the POSA would consider such disparate combinations, the POSA would be surprised by any success due to "nihilism" in the field after the failure of *six* prior clinical trials attempted to use PAH drugs to treat vulnerable PH-ILD patients, and the lack of any controlled study indicating a possible treatment effect for inhaled treprostinil.

2. Liquidia's theory that "prior sales" of Tyvaso invalidate the claimed methods of treatment is foreclosed by law. It is undisputed that Tyvaso was FDA-approved only for PAH, not PH-ILD, before the critical date. Further, Liquidia admits "without question" that "PAH" is "not covered by the asserted claims of the '327 patent." Liq. Br. at 37. That ends the inquiry. For example, even if Liquidia could establish that a Tyvaso "PH-ILD" sale had occurred—it cannot—the sale of a *product* cannot invalidate a *method claim* unless the product "embodies" the method and the two are "inseparable." The Court expressly invited Liquidia to address the specific question of whether the sale of a product with multiple uses necessarily invalidates a claimed method. Tr. 976:7-977:11. Liquidia failed to address the question because the answer is fatal: *BASF*.

3. Liquidia's "inherency" theory is also legally flawed. Liquidia asserts that the 2017 Study Description (DTX8) is the "same" as INCREASE, but that is demonstrably false. Both the dosing and patient populations are different. Liquidia's argument that a distinct unrun method inherently anticipates, even if it only benefits "one single patient," would turn decades of Federal Circuit precedent on its head. INCREASE which did not follow the prior art procedure alleged to inherently anticipate "cannot" prove inherent anticipation.

4. Liquidia's written description arguments turn on semantics not evidence. In short, Liquidia attempts to transform a single measurement taken of a single breath (FVC) into a *genus* just because that single breath measurement can be expressed as a *patient-specific* absolute expression and as a *normalized* expression. The inventors demonstrated possession of "FVC" based on INCREASE discoveries disclosed in the specification. Following Liquidia's logic, the POSA's ability to make standard conversions with known mathematical equations would transform any claim reciting results capable of being expressed in both metric units and U.S. units into a genus. Liquidia's baseless argument fails.

II. COUNTERSTATEMENT OF FACTS

A statement of facts is provided in Plaintiff's Proposed Findings of Fact ("PFF").

III. LEGAL STANDARDS

Liquidia, as the Defendant, bears the burden of proving each of its proffered invalidity defenses by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 102 (2011). UTC further addresses the applicable legal standards in the sections below.

IV. CLAIMS 5, 6, 9, AND 17 ARE ENTITLED TO PATENTABLE WEIGHT

Recognizing the flaws in its invalidity arguments, Liquidia seeks to raise new challenges to claims 5, 6, 9, and 17, arguing that they are not entitled to patentable weight. Liq. Br. at 1-3. Liquidia forfeited these arguments, and even absent forfeiture, its arguments are meritless.

A. Liquidia forfeited its patentable weight arguments

Liquidia forfeited its patentable weight arguments by failing to timely assert them. Indeed, Liquidia's Answer, four sets of Invalidity Contentions, and eight expert reports contain zero allegations relating to patentable weight. *See, e.g.*, D.I. 12. And Liquidia did not contend during claim construction that claims 5, 6, 9, and 17 were non-limiting, or identify lack of patentable weight as an elected invalidity defense. D.I. 123, 317, 318, 361. Instead, Liquidia buried this argument in a motion brought only two months before trial and expressly conditioned it upon the alleged "Infringement-Focused Construction of Drs. Nathan and Thisted." D.I. 283 at 13-17. The Court denied Liquidia's motion. D.I. 363. Liquidia also failed to raise this argument at the pretrial conference when the Court ordered additional claim construction briefing. Pretrial Conf. Tr. 29:15-38:8. Liquidia's failure to timely disclose its patentable weight defense significantly prejudiced UTC and denied UTC any meaningful opportunity to respond. A finding of forfeiture is clearly warranted here. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 641 (Fed. Cir. 2011); *Cent. Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Sols., P.C.*, 482 F.3d 1347, 1356 (Fed. Cir. 2007); *Kaufman v. Microsoft Corp.*, 34 F.4th 1360, 1369 (Fed. Cir. 2022); *In re Google Tech. Holdings LLC*, 980 F.3d 858, 862 (Fed. Cir. 2020) ("[T]he court mainly uses the term 'waiver' when applying the doctrine of 'forfeiture.'").

B. The dependent claims all have patentable weight

Liquidia's argument is facially flawed. Liquidia's willing stipulation of infringement of claims 1 and 14 but refusal to concede infringement of claims 5, 6, 9, and 17 demonstrates that those claims have patentable weight. Indeed, Liquidia's counsel conceded as much, telling the Court: "every single one of these claims -- 5, 6, 9, 17, and Claim 1 -- require some type of measurement or outcome to be observed. They require it." Tr. 947:5-8.

Claims 5, 6, 9, and 17 are unlike those considered in *BMS* and the other cases Liquidia

cites. Liq. Br. at 1. The majority of Liquidia's cases address whether a claim preamble is limiting, which the parties have already agreed to be the case (D.I. 155) and is not in question here. Nonetheless, Federal Circuit precedent addressing statements of intended purpose in methods of using compounds "has tended to result in a conclusion that such [] language is limiting." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1341-42 (Fed. Cir. 2021) (citing cases). Where claims were found to carry no patentable weight, the Federal Circuit has explained that "the language at issue identified a property in only very general terms and appeared in the very same claim that stated the other more concrete requirements." *L'Oréal USA, Inc. v. Olaplex, Inc.*, 844 F. App'x 308, 324 (Fed. Cir. Jan. 28, 2021). That is not what we have here. Like the claims in *L'Oréal*, "[t]he fairer understanding of [claims 5, 6, 9, and 17] is that they limit the options covered by the subject matter defined by the claim[] on which they depend to options that produce the concretely specified results—thus making a difference in the manipulative steps." 844 Fed. Appx. at 324. Each of claims 5, 6, 9, and 17 recite specific requirements not present in claim 1 that must be satisfied. The device, product, formulation, dosing, and course of treatment over time would all impact the results obtained when a patient administers according to the method in claim 1.

Further, Liquidia's reliance on Dr. Nathan's testimony is misplaced. Dr. Nathan did not say that *any* administration according to claim 1 would infringe claims 5, 6, 9, and 17. *Compare* Tr. 162:16-164:7, *with Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). Rather, Dr. Nathan explained that one specific product—*Yutrepia*—would infringe claims 5, 6, 9, and 17 if the method of claim 1 was performed because of (a) its equivalence with to Tyvaso and (b) the results of the INCREASE trial. Tr. 142:18-146:17, 95:19-96:25, 105:14-107:5, 117:17-19. He did not testify that *any* administration of inhaled treprostinil according to claim 1 would also practice claims 5, 6, 9, and 17. Tr. 162:16-164:7.

Finally, Liquidia argues that its burden of showing invalidity of claims 5, 6, 9, and 17 is

somehow negated because "no further step is needed to infringe these claims [and] the same interpretation is required for invalidity." Liq. Br. at 2. Not so. UTC has proven infringement as required in Hatch-Waxman cases: through the Yutrepia label and evidence of its equivalence to Tyvaso. Dr. Nathan considered claim 1 and separately considered the evidence regarding Yutrepia for the dependent claims. Liquidia's burden on invalidity remains; it must demonstrate invalidity not only of claim 1, but also the additional elements of claims 5, 6, 9, and 17.

V. THE '793 PATENT IS NOT PRIOR ART TO THE '327 PATENT

Liquidia's obviousness defenses, all of which rely upon the '793 patent, must fail as a matter of law because the '793 patent is not prior art to the Asserted Claims. Notably, obviousness is Liquidia's sole defense to claim 14, to which Liquidia has admitted infringement. Tr. 28:7-10.

A. Prior art is defined by 35 U.S.C. § 102

The America Invents Act ("AIA") amended 35 U.S.C. § 102(a) to read:

[a] person shall be entitled to a patent unless—

> (1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or
>
> (2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

35 U.S.C. § 102(a). Liquidia does not argue that the '793 patent, which published and issued *after* the undisputed effective filing date of the '327 patent, April 17, 2020, is prior art under § 102(a)(1). It is not. The relevant subsection here is § 102(a)(2).

The AIA further modifies what is prior art under § 102(a)(2): the "common ownership" exception under § 102(b)(2)(C) carves out any disclosure where "the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person." Thus, a reference

patent or patent application cannot be prior art under § 102(a)(2) where the reference was commonly owned on the effective filing date of the challenged patent—*even if* it was filed before that date. 35 U.S.C. § 102(b)(2)(C); M.P.E.P. §§ 717, 717.02; D.I. 398-1, Ex. C (*Sanofi Pasteur Inc. v. Pfizer, Inc.*, IPR2018-00188 (P.T.A.B. June 5, 2018)) at 13-15.

B. The '793 patent is not prior art under § 102(a)(2)

The '793 patent does not qualify as a "patent document" prior art under § 102(a)(2) because it falls within the § 102(b)(2)(C) common ownership exception. As above, this exception provides that patent documents that would otherwise satisfy § 102(a)(2) "shall not be prior art" if, "not later than the effective filing date of the claimed invention," "the subject matter disclosed and the claimed invention … were owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. § 102(b)(2)(C). Here, "the subject matter disclosed" is the '793 patent, and the "claimed invention" is the Asserted Claims. Because both were owned by UTC on April 17, 2020—the undisputed effective filing date of the '327 patent—the '793 patent "shall not be prior art" under § 102(a)(2). *Id.*; PFF 22.

1. UTC owns both the '793 patent and the '327 patent

UTC has owned both the '793 patent and the '327 patent since at least the effective filing date of the '327 patent, which satisfies the requirements of § 102(b)(2)(C).

'793 Patent: UTC has owned the '793 patent at all relevant times. UTC's Vice President of Global Regulatory Affairs, Dr. Noah Byrd, testified that UTC has "always owned" the '793 patent from the date it was "first filed." PFF 24. Liquidia does not dispute that UTC owned the '793 patent on the day it issued; indeed, UTC is listed as the "assignee" on the face of the patent. *Id.* Moreover, Liquidia has explicitly admitted in a prior litigation between the parties that UTC filed the application that issued as the '793 patent in January 2020. *Id.* It is thus undisputed that UTC owned the '793 patent, and any applications leading to it, at least from January 2020 onward,

including on the effective filing date of the '327 patent, Apr. 17, 2020. *Id.*

'327 Patent: UTC has also owned the '327 patent at all relevant times. Dr. Byrd testified that UTC has "always owned" the '327 patent from the date it was "first filed." PFF 25. Notably, Liquidia never explicitly alleges that UTC did not own the '327 patent on its effective filing date. Liquidia instead invites the Court to ignore Dr. Byrd's clear, unrebutted testimony and find that UTC failed to meet its burden of production on common ownership. Liq. Br. at 4-6. Liquidia's position is both legally deficient and wrong on the merits.

Liquidia's arguments hinge on unfair burden shifting. It is Liquidia's burden to prove invalidity by clear and convincing evidence, including the references it relies on constitute prior art under § 102. Thus, it was Liquidia's burden to demonstrate that the '793 patent is prior art and that no exceptions apply, e.g., that there was no common ownership. Liquidia utterly failed to do so and simply pretended the issue did not exist. On that basis alone, Liquidia's arguments fail, but even if UTC had the burden of invoking § 102(b)(2)(C), it clearly did so with unrebutted evidence.

First, Liquidia's argument that Dr. Byrd's testimony is unreliable borders on frivolous, especially since Liquidia chose not to cross-examine him on any of the points it now attacks. Liq Br. at 5-6. Dr. Byrd testified that he developed an understanding of UTC's patent portfolio as part of his regulatory role at UTC, making clear that his testimony on patent ownership was based on personal knowledge. Tr. 35:14-22. Dr. Byrd testified to those facts without objection, and Liquidia declined to cross-examine him on them. *Id.*; Tr. 39:96-41:16. Any objection to the foundation of Dr. Byrd's testimony is waived as untimely. *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, 2018 WL 2422003, at *2 (D. Del. May 29, 2018). *EcoFactor, Inc. v. Google LLC*, is inapposite because there—unlike here—the testifying witness admitted he lacked requisite personal knowledge. 137 F.4th 1333-34 (Fed. Cir. 2025). *Acceleration Bay LLC v. Activision Blizzard Inc.*, where the excluded testimony lacked foundation and the issue was properly

presented *in limine*, is likewise irrelevant. 2018 WL 5045186, at *1-2 (D. Del. Oct. 17, 2018).

Second, Liquidia's suggestion that Dr. Byrd's testimony related to the listing of patents in the Orange Book is wholly unsupported and strains credulity. Liq. Br. at 6. Dr. Byrd clearly testified that UTC has "always owned" the '327 patent from when it was "first filed." Tr. 36:13-24. Further, there can be no dispute that the '327 patent was "first filed" on Apr. 17, 2020, when the '810 provisional was filed. DTX0375.0049; *see Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1368 (Fed. Cir. 2011) (patentee "first filed a provisional patent application on [date]"). The record is clear: UTC has "always owned" its patents. PFF 24-25. Moreover, having failed to cross-examine Dr. Byrd on this issue, Liquidia cannot now claim that his testimony was somehow ambiguous or referred to anything other than ownership on the date of PTO filing.

Third, Dr. Byrd's testimony conclusively establishes the applicability of § 102(b)(2)(C). PFF 24-25. The M.P.E.P., on which Liquidia itself relies, provides that patent applicants seeking to invoke the § 102(b)(2)(C) exception need only state "'Application X and Patent A were, not later than the effective filing date of the claimed invention in Application X, owned by Company Z.'" and that "[t]his statement ***alone*** is sufficient to invoke the prior art exception under 35 U.S.C. 102(b)(2)(C)." M.P.E.P. § 717.02(a)(I)(B) (emphasis added). UTC plainly met this standard at trial through Dr. Byrd's testimony that UTC owned both the '793 and '327 patents since the day they were first filed. PFF 24-25. Moreover, Dr. Byrd's testimony is corroborated by record evidence that *Liquidia itself* moved to admit at trial over UTC's objection. The '810 provisional, for example, plainly identifies UTC as both the original applicant and the assignee on the day it was filed. DTX0375.0043. This creates an unrebutted presumption that, as of Apr. 17, 2020, UTC was the owner of the '810 provisional and any patent that issued from it. *See* 37 C.F.R. § 3.73(a). Any argument that Dr. Byrd or UTC must provide additional ownership evidence is contrary to the very M.P.E.P. sections on which Liquidia relies. Similarly, neither PTAB decision cited by Liquidia

(Liq. Br. at 7-10) stands for the proposition that assignment documents are *required* to invoke the § 102(b)(2)(C) exception. Nor could they, given specific guidance from the USPTO to the contrary. M.P.E.P. § 717.02(a)(I)(B). Liquidia's failure to challenge the evidence at trial is fatal to its *post hoc* argument. Indeed, Liquidia has not offered any evidence that UTC did not own either the '327 patent or the '810 provisional as of Apr. 17, 2020. The face of the '810 provisional identifies UTC as both the applicant and the assignee, and Liquidia has pointed to nothing that would suggest otherwise. This is because, as Dr. Byrd testified, UTC has always owned the '327 patent since the day it was first filed as the '810 provisional. Tr. 36:13-24.

2. The '793 patent is not admitted prior art

Having failed to prove that the '793 patent is prior art to the '327 patent under § 102, Liquidia argues the Court should nonetheless consider the '793 as "admitted prior art." Liq. Br. at 9-11. Liquidia's fails for at least four independent reasons, discussed below.

Liquidia waived its admitted prior art theory: Liquidia raised the issue of admitted prior art for the very first time during closing argument at trial and did not offer any evidence on the subject. Tr. 914:7-14. Indeed, Liquidia admitted in the Pretrial Order that one of the "issues of law remaining to be litigated" was whether Liquidia had proven the '793 patent was *statutory* prior art under 35 U.S.C. § 102(a). D.I. 335-1 at ¶ 61. Liquidia had no intention of arguing that the '793 patent was "admitted" prior art and never stated that the *issue* of admitted prior art was relevant to the case at all. *Id.* It is not. Nonetheless, "[l]egal theories and issues not raised in the pretrial order are considered waived." *Gavrieli Brands LLC v. Soto Massini (USA) Corp.*, 2020 WL 1443215, at *7 (D. Del. Mar. 24, 2020) (quotation marks omitted). Liquidia drafted its portion of the pretrial order with full knowledge of both (i) UTC's intent to challenge the prior art status of the '793 patent; and (ii) the supposed "admissions" it now raises for the first time. PFF 23. Liquidia's admitted prior art theory is therefore waived. *See Gavrieli*, 2020 WL 1443215, at *7.

Liquidia's Argument Fails on the Merits: No statements made during prosecution of the '327 patent or in its specification render the '793 prior art. Liq. Br. at 9-10. Liquidia ignores well-settled law holding that merely incorporating a reference during prosecution of a patent does not amount to an admission that the reference is "prior art." *See Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1279 (Fed. Cir. 2003); *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1355 (Fed. Cir. 2003). Indeed, Liquidia's cases actually stand for the proposition that an applicant must *do more* than merely cite or incorporate a document in order to "admit" that it is prior art. For example, the admission in *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, included statements from the *background of the invention* section of the specification that certain elements had "been identified," "been demonstrated," "been shown," and "been reported." 491 F.3d 1342, 1361-62 (Fed. Cir. 2007). No such admission exists here. Liquidia points to a single sentence in the specification of the '327 patent which incorporates by reference the UTC-owned '793 patent. That sentence states: "Pulsed inhalation devices are disclosed … in U.S. Pat. Nos … 10,716,793, each of which is incorporated herein by reference in its entirety." JTX-0001-00033, 20:48-57; Liq. Br. at 9-10. Notably, the '793 patent had not yet issued when the '810 provisional was filed on Apr. 17, 2020, but it had issued at the time the '327 patent specification was filed as part of a non-provisional application one year later on April 16, 2021. *Id.* In April 2021, a *present-tense* incorporation of the '793 patent conveys nothing about its prior art status for the '327 patent with a priority date of April 2020. *See Riverwood*, 324 F.3d at 1355 ("the patentee should not be punished for … referencing his own work"). Liquidia's suggestion that Dr. Nathan "confirmed this admission" by reading the plain text of the specification on cross-examination adds nothing to the relevant analysis. Liq. Br. at 9-10; Tr. 895:19-896:5.

UTC Made No Prior Art Admissions In This Litigation: At every stage in this litigation, UTC has consistently and repeatedly made clear the '793 patent itself is not prior art. PFF 23.

Liquidia, however, points to three supposed "admissions" from the preliminary injunction stage of these proceedings—(1) a statement by UTC counsel during the P.I. hearing, (2) UTC's P.I. briefing, and (3) Dr. Nathan's response to Liquidia's defeated inequitable-conduct allegations—but none actually states that the '793 patent is prior art. Liq. Br. at 10. Nor are these statements binding, because whether a reference falls within § 102(b)(2)(C) is "an issue of law, not a fact susceptible of admission." *Gov't Emps. Ret. Sys. of Virgin Islands v. Gov't of Virgin Islands*, 995 F.3d 66, 95 n.28 (3d Cir. 2021). Further, as this Court has made clear, arguments made during the P.I. stage do not create binding "law of the case." Pretrial Conf. Tr. at 57:24-58:8.

None of the statements Liquidia points to constitute an "admission" that the '793 is prior art. First, UTC counsel's statement during the P.I. hearing that "the disclosure" of the '793 patent might be prior art is not equivalent to an admission that *the asserted document itself* is prior art. P.I. Hearing Tr. at 22:18-22. The full context of those statements—which Liquidia ignores—makes clear UTC's position: "for the purposes of today, let's assume that [the '793 patent] is prior art." *Id.* Issued patents contain both a specification and claims, and Liquidia relies on both to argue obviousness. DFF 30, 34, 69. Second, Dr. Nathan's statement that the '793 patent was identified by the examiner in a "prior art *search*" is far from an admission by *UTC* that the '793 patent is prior art under § 102. D.I. 28 at 37. Examiners routinely review co-pending applications during prosecution, and the fact that the '793 patent appeared in such a search does not make it prior art. Third, Liquidia is incorrect that Dr. Nathan's opinions or UTC's briefing regarding cumulativeness in the context of inequitable conduct are "irrelevant if the '793 patent is not prior art." Liq. Br. at 10 (citing D.I. 28; 239). These opinions and statements—at most—establish that the '793 patent "may [have] be[en] material to prosecution of the pending claims." *Abbott*, 334 F.3d at 1279.

"Admitted Prior Art" Is Contrary to the AIA: Finally, the judge-made doctrine of "admitted prior art" should not apply to patents issued under the AIA, where it is displaced by a

clear statutory command that certain references "shall not be prior art." 35 U.S.C. § 102(b)(2). "[W]hen Congress addresses a question previously governed by a decision rested on federal common law the need for such an unusual exercise of lawmaking by federal courts disappears." *City of Milwaukee v. Illinois & Michigan*, 451 U.S. 304, 314 (1981). The doctrine of admitted prior art arose under the pre-AIA framework, where sources of prior art were scattered between § 102 and § 103. *In re Nomiya*, 509 F.2d 566, 570 n.5 (C.C.P.A. 1975). However, in the AIA, Congress "redefined what constitutes 'prior art' against a patent or application," creating a unified definition for both anticipation and obviousness. *SNIPR Techs. Ltd. v. Rockefeller Univ.*, 72 F.4th 1372, 1375 (Fed. Cir. 2023); M.P.E.P. § 2152. Liquidia therefore cannot deploy the antiquated, judge-made "admitted prior art" doctrine against the '327 patent, which issued under the AIA.

C. Liquidia's obviousness combination fails

Liquidia's obviousness defense cannot succeed without the '793 patent. Where a challenger relies on a document that is ultimately determined not to be prior art, the obviousness combination fails. *See, e.g.*, *Medtronic, Inc. v. Teleflex Innovations S.À.R.L.*, 68 F.4th 1298, 1308 (Fed. Cir. 2023); *Janssen Pharms., Inc. v. Tolmar, Inc.*, 718 F. Supp. 3d 394, 412 (D. Del. 2024). Nothing in Faria-Urbina 2018 or Saggar 2014 fills the gap left by omission of the '793 patent. Indeed, the reason Liquidia relies on the '793 patent is that the other references say nothing about a dry powder formulation or its use. Tr. 474:14-475.

Liquidia attempts to square this circle by pointing to other prior art references that purportedly contain the same disclosures as the '793 patent, such as the '507 patent (DTX-0062) and WO2019/237028, which is not even a trial exhibit. Liq. Br. at 15-16. However, Liquidia did not identify any of these substitute references in the obviousness combination it disclosed prior to trial. D.I. 361. Liquidia also failed to elicit any testimony at trial as to how these substitute references might render the Asserted Claims obvious. In fact, Liquidia did not even attempt to

introduce the '507 patent into evidence until the cross examination of *UTC's* final rebuttal expert, Dr. Nathan. Tr. 896:17-898:15. The Court should not permit Liquidia to substitute the '507 patent (or any other reference) in place of '793 patent. Not only would that effectively allow Liquidia to create a new defense contrary to the Court's previous orders (D.I. 317, 318), but there is no factual support for such a defense in the trial record. Liquidia made the strategic choice to rely on the '793 patent—including its claims—to prove obviousness. Indeed, Liquidia argues that UTC should be collaterally estopped from arguing non-obviousness of treprostinil DPI formulations based this Court's prior decision that the *claimed subject matter* of the '793 patent was enabled. Liq. Br. at 16-17. Liquidia could not make this argument if it were merely relying on the "disclosure" of the '793 patent. *Cf. Id.* at 16. Liquidia must live with the consequences of its decision.

VI. THE ASSERTED CLAIMS ARE NOT OBVIOUS

Liquidia's obviousness case hinges on hindsight and cherry-picking allegedly positive results from pilot studies. Liquidia—armed with *post hoc* knowledge of the INCREASE results—asserts that the POSA would have ignored the preceding fifteen years of failure and expected inhaled treprostinil to be uniquely successful. Liquidia nevertheless points to the small, uncontrolled studies disclosed in Faria-Urbina 2018, the '793 patent, and Saggar 2014, and asks the Court to draw conclusions far beyond what these references' expert authors explicitly concluded at the time. Without impermissible hindsight, these studies could not provide the POSA with a motivation to combine or a reasonable expectation of success. Indeed, Liquidia's own CMO admitted that UTC made a "bold move" by even *pursuing* INCREASE. Tr. 50:16-51:3. Bold action reflects risk and innovation, not obviousness.

A. The use of Group 1 PAH therapies for PH-ILD was controversial

Liquidia's hindsight-driven obviousness theory fails because it requires the POSA to ignore the clear headwinds in the PH-ILD field as of April 2020. Despite serial attempts, no drug

had ever been approved to treat any form of Group 3 PH, including PH-ILD. PFF 2, 26; *infra* § VI.D. Attempting to treat PH-ILD patients with PAH therapies at this time was highly controversial, even among the most experienced clinicians. PFF 26, 29-31. As a result, influential treatment guidelines actively cautioned *against* using Group 1 PAH drugs—including treprostinil—in PH-ILD. PFF 30. Even Liquidia's references in this case cautioned *against* using treprostinil in PH-ILD—an instruction the POSA would have taken to heart. PFF 29; *Infra* § VI.B.

1. An "impossible dream": failed trials fueled skepticism in the field

The POSA's reluctance to use PAH drugs in PH-ILD patients would have been fueled by the field's consistent and continued failure to validate this treatment concept in a controlled trial. PFF 26-27, 29-30; *infra* § VI.D. Between 2007 and 2019 *six* double-blind, multicenter, placebo-controlled, randomized trials were conducted to investigate whether pulmonary vasodilators approved for Group 1 PAH could safely and effectively treat PH-ILD patients: ACTIVE (Iloprost), STEP-IPF (Sildenafil), ARTEMIS-IPF (Ambrisentan), BPHIT (Bosentan), INSTAGE (Nintedanib and Sildenafil), and RISE-IIP (Riociguat). PFF 26-27. Each time doctors hoped for success. *Infra* § VI.D. But all were negative, and ARTEMIS-IPF and RISE-IIP were stopped early for safety reasons. PFF 26-27; *infra* § VI.D. Liquidia attempts to minimize the state of the art (Liq. Br. at 14-15), but the POSA would have paid close attention. PFF 26. Dr. Nathan was involved in all six trials, including as chair of the RISE-IIP steering committee. PFF 26. He testified that these failures created "widespread skepticism" in the field regarding the use of PAH drugs in PH-ILD and that the "prevailing, overwhelming feeling" was that this treatment concept risked patient harm. PFF 26; *infra* § VI.D. Similarly, Dr. Franck Rahaghi—a paid advisor to Liquidia—concluded that "[n]one of this stuff really worked, and so this created a kind of nihilism on the part of the community [of ILD physicians]." PFF 26. The POSA would thus have been skeptical of deploying PAH therapies in PH-ILD patients. PFF 26; *infra* § VI.D.

RISE-IIP terminating on safety grounds had a particularly negative impact on the field. PFF 26. In fact, Dr. Lewis Rubin—a '793 patent inventor and luminary in the field—publicly admonished Dr. Nathan when he presented the results of RISE IIP at a European Respiratory Society meeting. PFF 26. In no uncertain terms, Dr. Rubin stated: "everyone knows that treating PH associated with ILD does not work." *Id*. This was not an isolated incident. PFF 26. Dr. Wertheim also emphasized the devastating impact of RISE-IIP on the field, testifying that the POSA would have already been wary of PAH drugs in view of failed studies like ARTEMIS-IPF, and he confirmed that the failure of the RISE-IIP created a sense of "nihilism." PFF 26-27. Dr. Wertheim explained that he was "skeptical that [there] was ever going to be a PAH-specific therapy that that would show efficacy in PH-ILD," analogizing the failed trials to climbers that died in their attempt to climb a mountain that was no less dangerous as of April 2020. PFF 26-27. Dr. Wertheim was not alone—the prior art literature directly questioned whether the use of *any* PAH drug in PH-ILD could be justified, and as a result, whether the overall concept was an "impossible dream." PFF 26. This is the definition of industry skepticism.

Dr. Nathan explained that RISE-IIP also forced the PH-ILD field to reckon with the inherent unpredictability of uncontrolled "pilot studies" used to justify larger clinical trials in this patient population. PFF 27. Indeed, promising pilot data preceded each of the six failed PH-ILD trials discussed above. PFF 27. RISE-IIP was particularly concerning in this respect because it was based on a high-quality *prospective* pilot study by Hoeper et al. (PTX-0436), which was published in a top-tier pulmonary journal and seemingly reported a clear signal of potential benefit without safety concerns. PFF 27. The POSA would have found another cautionary tale in the PANTHER-IPF trial, which investigated a three-drug cocktail that over 50% of pulmonologists were prescribing to IPF patients based merely on uncontrolled pilot data and anecdotal accounts. PFF 27. PANTHER-IPF—to the shock of the field—revealed that this cocktail not only lacked

efficacy but was associated with an increased risk of hospitalizations and death. PFF 27. Accordingly, the POSA would know from PANTHER-IPF, RISE-IIP, and other failed trials that data from uncontrolled studies should be viewed with skepticism. PFF 27.

The POSA's skepticism of pilot studies and anecdotal reports in PH-ILD would have been reinforced by their training in biostatistics. PFF 27-28. As a general rule, studies without systematic controls lack predictive value for establishing a treatment effect, i.e., that an effect is due to the treatment and not some other cause. PFF 27. Anecdotal accounts similarly lack predictive value because they are unverifiable, lack scientific rigor, and are limited by subjective impressions and confirmation bias. PFF 27. The POSA would also recognize that controlled study data are even more necessary when—as in PH-ILD—the disease being investigated exhibits high patient-to-patient variability. PFF 27. The documented unreliability of pilot studies and anecdotal reports in PH-ILD, would have further reinforced these fundamental biostatistics concepts to the POSA. PFF 28.

2. The POSA would not have used inhaled treprostinil in PH-ILD

Liquidia argues that the decade of failed trials that preceded April 2020 would not have dissuaded the POSA from using treprostinil in PH-ILD because all of those trials used other drugs. Liq. Br. at 14-15. However, this theory is contrary to the clear consensus in the medical literature as well as how doctors of ordinary skill were actually treating PH-ILD. PFF 26, 29-31.

The six failed trials discussed above tested every class of pulmonary vasodilators—including the inhaled prostacyclin class to which treprostinil belongs—which treat hypertension by expanding blood vessels. PFF 26.[1] The breadth of this failure was recognized in the medical literature, cautioning against the use of PAH therapies *generally*. *Supra* § VI.A.1; PFF 26, 29-30.

[1] ACTIVE, the first failed trial of a PAH therapy in PH-ILD, involved inhaled iloprost, a prostacyclin belonging to the same class of drugs as treprostinil. Tr. 85:10-18; PFF 26.

For example, the treatment guidelines published by the 6th World Symposium on Pulmonary Hypertension[2] in 2019 expressly cautioned against using PAH medications—including treprostinil—in PH-ILD patients due to the lack of reliable clinical data:

> Riociguat and ambrisentan are both contraindicated in IIP-PH. There is no evidence of benefit for other endothelin receptor antagonists in IIP-PH. Data on the use of sildenafil in IIP-PH is conflicting, while evidence for prostanoid therapy is too limited for any current recommendations. Further RCTs are encouraged.

PFF 30. Consistent with this guidance, the POSA would have been skeptical that inhaled treprostinil would be safe and effective in PH-ILD. *Supra* VI.A.1; PFF 26, 29-30.

The Court heard testimony about the real-world practice of Drs. Wertheim and Parikh, both of whom had experience consistent with that of the POSA in April 2020. PFF 31. Neither testified that they had confidence in treprostinil as a PH-ILD therapy in April 2020. PFF 26-27, 31.

Dr. Wertheim, who trained at Brigham and Women's Hospital, recounted the pessimism in the field as of April 2020. *Supra* § VI.A.1; PFF 31. Dr. Wertheim also explained that the field "put a lot of weight" in the 6th World Symposium Guidelines as of April 2020. *Supra* § VI.A.1; PFF 30-31. Consistent with these guidelines, Dr. Wertheim was trained *only* to prescribe inhaled treprostinil to patients that were adjudicated to have Group 1 PAH, whereas PH-ILD patients received "supportive care" targeting the underlying lung disease. PFF 30-31. Dr. Wertheim revealed that the stakes were high when patients presented with symptoms of both PH and ILD, detailing his evidence-based concern that pulmonary vasodilators would harm PH-ILD patients—a concern the POSA would have shared. *Supra* § VI.A.1; PFF 31.

Dr. Parikh was a fellow at Duke Medical Center as of the relevant time. PFF 31. He testified that to the extent any PH-ILD patients received treprostinil at Duke, it was only those classified as having "out of proportion pulmonary hypertension that had a component of PAH" and that Duke

[2] Dr. Nathan co-chaired the task force that drafted these guidelines; '793 patent inventors Horst Olschewski and Werner Seeger were also authors, and Dr. Rubin was an editor. PFF 30.

was likely "more aggressive" in its approach as compared to other hospitals. PFF 31. However, Dr. Parikh made clear that "the classification of these patients is messy," and that he only prescribed treprostinil to treat the *PAH component of their disease*—not their PH-ILD. PFF 31. Dr. Parikh and his colleagues were therefore using treprostinil *on-label* to treat PAH, not off-label to treat PH-ILD. Dr. Parikh indicated that the utility of treprostinil in these patients was a "much greyer area at that time" due to a lack of reliable data. PFF 31.

3. Liquidia's allegations of off-label use ignore the POSA's perspective

Liquidia attempts to bolster its obviousness position by pointing to the alleged off-label prescribing practices of five expert clinicians—Richard Channick, Nicholas Hill, Victor Tapson, Aaron Waxman, and Rajan Saggar. *See, e.g.*, Liq. Br. at 12-15, 17-19; DFF 36-37, 60, 78, 85, 92, 101, 109, 119-122. However, Liquidia's selective account of these doctors' testimony is both inaccurate and legally irrelevant. Each of these individuals had a degree of skill that far exceeded that of the POSA—they were experts in the field and ran highly specialized practices. PFF 31. Three of the five doctors—Drs. Saggar, Tapson, and Waxman—were fact witnesses and thus *did not even attempt* to testify from the perspective of the POSA. Further, because much of the alleged off-label use was never published or contemporaneously documented, Liquidia must rely on uncorroborated post-priority testimony that would not have been available to the POSA. *Infra* § VII; PFF 63, 64; s*ee, e.g.*, DFF 36-37, 60, 78, 85, 92, 101, 109, 119-122. Liquidia's theory is thus detached from the POSA's perspective, and instead improperly relies on those of extraordinary skill. PFF 31. However, obviousness must be determined "from the viewpoint of one of ordinary, not extraordinary skill." *Rotron, Inc. v. U.S. Int'l Trade Comm'n*, 845 F.2d 1034 (Fed. Cir. 1998); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1339-40 (Fed. Cir. 2010).

The relevant inquiry here is not what the leaders in the field were doing *behind closed doors*, but how the POSA would have approached the use of treprostinil in PH-ILD as of the

priority date. The POSA would not have ignored a decade of failed trials, the literature in the field, consensus treatment guidelines, or their medical training—each of which would have been sufficient to inform the POSA not to expect inhaled treprostinil would be a successful PH-ILD intervention. *Supra* §§ VI.A.1,VI.A.2. To the contrary, the balance of available evidence would give the POSA concerns that the drug could be harmful. *Supra* §§ VI.A.1,VI.A.2; *infra* §§ VI.B, VI.C, VI.D. Further, even if Liquidia's allegations of prior off-label use are taken at face value, they represent a practice that would have been well outside of the mainstream in April 2020. *Supra* §§ VI.A.1,VI.A.2. The POSA would know that using *any* PAH drug in Group 3 PH was a highly controversial concept, *id.*, and to the extent such use did occur, the vast majority of reports in the literature focused on PDE5 inhibitors like sildenafil and tadalafil. PFF 30. In fact, the two peer-reviewed literature references that did mention inhaled treprostinil in this context—Faria-Urbina 2018 and Parikh 2016—did not recommend off-label use and instead called for caution and further studies. *Infra* § VI.B.1; PFF 29, 47. There is also no evidence that any of the doctors Liquidia relies on were publicly encouraging others to use inhaled treprostinil in PH-ILD. To the contrary, several of them recommended *against* such off-label use.

Rajan Saggar: Despite claiming to have used treprostinil in PH-ILD patients frequently prior to April 2020, Dr. Rajan Saggar's published work tells a very different story. PFF 29. Dr. Saggar's publications consistently characterize the use of treprostinil and other PAH medications in PH-ILD as "controversial," "not [] well studied," supported by "limited evidence," and "discouraged" by leading treatment guidelines due to safety concerns and a lack of efficacy data—far from an encouragement for the POSA to use treprostinil in PH-ILD.[3] PFF 29. In fact, Saggar 2014, a key component of Liquidia's obviousness position, expressly cautions the POSA *against*

[3] In a 2024 podcast recorded before his involvement in this litigation, Dr. Saggar recited the numerous failures that preceded INCREASE and described Tyvaso as a "recent" arrival in the treatment of PH-ILD that "luckily" succeeded. PFF 29.

using PAH drugs in PH-ILD and emphasizes the limitations of the data it reports:

> "[a]t this point, the routine use of PH-targeted therapy in PF-PH is **[1]** *not recommended* and should **[2]** *only be cautiously considered* at **[3]** *specialized* PH centres to **[4]** *avoid the serious potential for worsening cardiopulmonary status in this patient population* … These findings are **[5]** *only hypothesis generating* and **[6]** *require* confirmation in a multi-centre, randomized study design … given **[7]** the *high mortality inherent in this population*, a future study may consider survival as an endpoint."

DTX0010.0006 (enumeration and emphasis added), *infra* § VI.B.3; PFF 29. These *seven* admissions showcase Liquidia's hindsight and directly undercut its obviousness story.

Aaron Waxman: Liquidia hails Dr. Waxman as a major proponent of using inhaled treprostinil in PH-ILD prior to April 2020. Liq. Br. at 13-14. However, Dr. Waxman's sole peer-reviewed publication on the topic, Faria-Urbina 2018, takes a much more conservative approach—offering an unequivocal caution against using PAH drugs in Group 3 patients:

> The potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies. Until then, its use in *Group 3 PH* should be *cautiously evaluated* in *specialized PH Centers* after an individualized assessment and risk–benefit consideration

DTX0518.0006 (emphasis added); *infra* § VI.B.1; PFF 29. The primary author of this paper, Dr. Mariana Faria-Urbina, confirmed that the authors' discussion of potential "therapeutic option[s]" in Group 3 PH was merely a "hypothesis" and "not an affirmation or recommendation." PFF 38. Indeed, Dr. Waxman was "petrified" before he received the INCREASE results. PFF 54.

Victor Tapson: Dr. Tapson testified that any use of PAH drugs in patients with PH-ILD was an "experimental" aspect of his practice that was not routine and required caution. PFF 29. Dr. Tapson is an author of the Parikh 2016 study, which states that inhaled treprostinil "has not been FDA approved for WHO groups II–V"; "the study … only included patients thought to be good candidates for higher dose iTRE"; that "[t]here were insufficient follow-up data to analyze efficacy endpoints"; and that "the results warranted further investigation." PFF 29, 47. Parikh 2016 would not encourage the POSA to try inhaled treprostinil in PH-ILD. PFF 47.

Richard Channick & Nicholas Hill: Liquidia did not present any evidence of Drs. Channick or Hill encouraging those of ordinary skill to use treprostinil in PH-ILD patients.

Steven Nathan & Lewis Rubin: Liquidia failed to account for the opinions and publications of Drs. Nathan and Rubin—both of whom were established leaders in the PH-ILD field as of April 2020. *Supra* §§ VI.A.1,VI.A.2; PFF 26, 30. Neither used treprostinil in PH-ILD patients prior to April 2020, and the evidence at trial demonstrated that both explicitly recommended *against* doing so. *Supra* §§ VI.A.1,VI.A.2.

B. Liquidia's cited prior art does not teach or suggest the claimed methods

Liquidia elected to assert a single obviousness defense consisting of three references: Faria-Urbina 2018, the '793 patent, and Saggar 2014. D.I. 361. None, alone or in combination, render the claims obvious. The clinical data reported in each is of insufficient quality or reliability to create a motivation—much less a reasonable expectation of success—that treprostinil could safely and effectively improve exercise capacity in PH-ILD patients, and these deficiencies are even more acute with respect to the clinical limitations required by the asserted claims 5, 6, 9, 14, and 17.

1. Faria-Urbina 2018

Liquidia greatly overstates the significance of the retrospective, uncontrolled clinical data reported by Faria-Urbina 2018. The POSA, in contrast, would immediately recognize that Faria-Urbina 2018 has serious flaws, both in terms of its study design and the results it reports. Consequently, the POSA would have found the data in Faria-Urbina 2018 to have been unreliable and unpersuasive in terms of the therapeutic potential of inhaled treprostinil in PH-ILD.

Flawed Study Design: Faria-Urbina 2018 has fundamental flaws that would preclude the POSA from drawing any firm conclusions from the resulting data. PFF 27, 33, 38. Critically, Faria-Urbina 2018 is a single-center, open-label, retrospective, uncontrolled study, meaning that it was conducted by performing a historical "chart review" of medical records and lacked a control group.

PFF 33. Further, patients who did not perform well on inhaled treprostinil were systematically excluded from the patient population, which prejudiced the results. PFF 35. These and other flaws would indicate to the POSA that the data reported by the study lacked predictive value as to the treatment effects of treprostinil and was, at best, hypothesis generating. PFF 38.

At the outset, the POSA would have been reluctant to draw any significant conclusions from a small, uncontrolled, retrospective chart review. PFF 27, 33. The POSA would have known the dangers of relying on small pilot studies, especially in PH-ILD. *Supra* § VI.A. For example, Dr. Parikh testified that retrospective studies "are weaker than prospective studies and randomized controlled trials because there are confounders… that can bias the results of the study." PFF 33. Dr. Parikh further noted that "evidence-based medicine," not anecdotal evidence, was required to determine whether a drug was suitable in a certain patient population. *Id*. Dr. Wertheim reached a similar conclusion. PFF 27, 33. Finally, as Dr. Nathan testified, the Hoeper pilot study that led to the failed RISE-IIP trial was of substantially higher quality than Faria-Urbina 2018. PFF 35.

The POSA would immediately recognize that, as a retrospective chart review, Faria-Urbina 2018 reports on information the authors obtained from medical records of patients they did not actually treat. PFF 33, 34. It is therefore unclear whether the paper's description of patients as having "Group 3" PH in association with one of three lung diseases (COPD, ILD, and CPFE) was based on the original diagnosis of the treating physician or a *post-hoc* determination made by the study authors. *Id*. Accordingly, Faria-Urbina 2018 does not provide the POSA enough information to verify which of the patients in the study actually had PH-ILD, i.e., PH that was at least in part due to their ILD. PFF 34. This is a significant concern because all of the results in Faria-Urbina are reported on a population basis rather than individually. PFF 35, 36. In other words, if not all of the patients in a given dataset actually had PH-ILD, this would significantly limit the POSA's ability to draw conclusions about treatment effects in PH-ILD because the POSA could not be sure

which patients were experiencing which effects. PFF 36.

Dr. Nathan testified that based on his review of Faria-Urbina 2018, it was possible that some of the patients classified as having "ILD" or "CPFE" were actually Group 1 PAH patients. PFF 34. For example, Dr. Nathan pointed to the hemodynamic data reported for two of the "ILD" patients as being compatible with PAH, but not PH-ILD. *Id*. These concerns were validated by Dr. Wertheim, who at the relevant time was working at the same PVD Clinic that treated the patients studied in Faria-Urbina 2018. PFF 31, 34. At that time, this clinic's prevailing practice was to *avoid* giving Tyvaso to PH-ILD patients, and to only use it in PAH. PFF 31. Dr. Wertheim concluded that some of the "PH-ILD" patients in Faria Urbina 2018 may have originally been diagnosed with PAH by the treating physician but then retrospectively re-categorized for purposes of the study. PFF 33, 34. This raises serious questions about the reliability of Faria-Urbina 2018.

Another critical flaw in Faria-Urbina 2018 was the authors' selective exclusion of patients who did not perform well on inhaled treprostinil. PFF 35. For example, individuals who experienced recent hospitalizations, received lung transplants, and were placed on additional therapy were all excluded. *Id*. The POSA would therefore recognize that any clinical results reported from this population would be skewed or biased in favor of positive results. *Id*. Moreover, while the authors of Faria-Urbina 2018 excluded patients who were started on new medications during the treatment period, they notably *did not* exclude patients who were already taking other PH medications before receiving treprostinil. *Id*. The presence of study participants taking multiple medications would, again, limit the POSA's ability to interpret the reported data because they would not know which drug was producing any observed effects. *Id*. In sum, the authors' decisions regarding what patients to include and exclude in the study would have made it very difficult for the POSA to draw any meaningful conclusions about the data reported. PFF 35, 38.

Flawed Results: The presentation of the clinical results in Faria-Urbina 2018 further

underscore their unreliability. For example, the paper obscures any disease-specific effects by aggregating data from patients with ILD, CPFE, and COPD. PFF 36. Consequently, the POSA is unable to discern the impact of inhaled treprostinil on PH-ILD patients specifically. *Id*. Moreover, while the paper's supplementary materials attempt to disaggregate the reported results by lung disease, there is not enough data for the POSA to draw meaningful conclusions with respect to key clinical endpoints like 6MWD. PFF 35, 36. Tables S3 and S4 in the supplemental materials report that of the 9 "ILD" and 5 "CPFE" patients studied, only 3 from each cohort recorded 6MWD results. PFF 35, 36. This discrepancy represents yet another potential source of selection bias. PFF 35, 36. Even taken at face value, the dataset is simply too small to allow the POSA to draw conclusions about the effects of inhaled treprostinil in the broader PH-ILD population. PFF 36, 38. This lack of predictability is underscored by the authors' conclusion that PH-COPD patients appeared to benefit the most, a hypothesis later disproven by the failed PERFECT study. PFF 38.

Liquidia argues that Faria-Urbina 2018, in particular its 6MWD results, establishes that inhaled treprostinil improves exercise capacity in PH-ILD patients. Liq. Br. at 11-12. However, the POSA would have known that these 6MWD results are based on a highly selected population that does not isolate effects in PH-ILD. PFF 35, 36. Of the 3 "ILD" and 3 "CPFE" patient cohorts, only the latter cohort shows a statistically significant improvement. PFF 35, 36. Even if the POSA assumed that each of these 6 patients had PH-ILD—which, as above, was far from certain—this limited dataset would not reasonably inform the POSA about the expected effects of inhaled treprostinil in PH-ILD more generally. PFF 36, 38. Faria-Urbina 2018 also reported that in the overall, ILD, and CPFE populations, patients saw *reductions* in both their forced vital capacity (FVC) and post-6MWT oxygen saturation (SpO_2), which would give the POSA concerns that the patients got sicker, thereby nullifying any potential benefits. PFF 37. Tellingly, the authors concluded that their results "should be further assessed in larger prospective studies" and cautioned

against using treprostinil in Group 3 PH patients outside of "specialized PH centers." PFF 38. Liquidia thus asks the POSA to draw conclusions far beyond those of the authors themselves.

Finally, the evidence at trial established that Faria-Urbina 2018 did not meaningfully impact the field. Dr. Wertheim testified that the paper did not change treprostinil prescribing practices at the PVD Clinic, and that he was not even aware of it prior to this litigation. PFF 31. Dr. Nathan noted that Faria-Urbina 2018 was published in a "lower-tier type of journal" and that he also did not learn of the paper until after April 2020. PFF 35. Indeed, Faria-Urbina 2018 is entirely absent from the 6th World Symposium's comprehensive review of Group 3 PH, published in 2019. PFF 30, 38. Liquidia nevertheless maintains that Faria-Urbina 2018 matters because "Dr. Waxman's work was the rationale and motivation to perform INCREASE." Liq. Br. at 13-14. However, former UTC scientist Kevin Laliberte—who attended Dr. Waxman's 2015 presentation at UTC and worked on INCREASE—testified that "because of the limited data set" and other limitations, he "had concerns moving forward into a larger study" and was "unsure" of what would happen, especially given that most of the clinical benefits observed by Dr. Waxman appeared to come from patients with PH-COPD (who were not part of INCREASE).[4] PFF 33, 55. Inventor Peter Smith testified similarly—while Dr. Waxman's results were "hypothesis-generating," they provided the field little confidence that INCREASE would be successful. PFF 55.

2. '793 Patent

Liquidia primarily relies on the '793 patent for its disclosure of a dry powder inhaler (DPI) formulation of treprostinil. (Liq. Br. 15-16). However, Liquidia ignores that the '793 patent and the '327 patent cover different subject matter and are directed to different POSAs.

The '793 patent is generally directed to methods of treating pulmonary hypertension via

[4] There were only *eight* PH-ILD patients in Dr. Waxman's dataset; these results did not give Dr. Laliberte confidence that INCREASE would succeed. PFF 38; Tr. 318:21-319:20.

administration of "a therapeutically effective single event dose" of inhaled treprostinil. DTX0002.0025. In a prior litigation between the parties, this Court held that (i) the claims of the '793 patent covered treatment of all five groups of pulmonary hypertension; (ii) that term "therapeutically effective single event dose" means "a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR)"; and (iii) the claims *did not* require "a method of safely and effectively treating pulmonary hypertension." *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 461, 465-69 (D. Del. 2022). The '793 patent therefore covers the use of single doses of inhaled treprostinil to improve *hemodynamics* in PH patients generally without any regard for safety or efficacy. PFF 40. This is fundamentally different from the Asserted Claims of the '327 patent, which cover methods of *improving exercise capacity* in PH-ILD patients. *Id*. Further, the two patents have different POSAs—the '793 patent's POSA could be *either* a PH clinician *or* pharmaceutical formulator while the '327 patent's POSA may only be a clinician with experience treating PH-ILD. *Compare United Therapeutics*, 624 F. Supp. 3d at 464 *with* Tr. 432:3-90, 895:6-18.

Against this background, the '793 patent in no way cures the significant deficiencies of Faria-Urbina 2018 or Saggar 2014. It is undisputed that the '793 patent is silent with respect to every one of the clinical endpoints required by the Asserted Claims: exercise capacity, 6MWD, NT-proBNP plasma concentration, exacerbations of interstitial lung disease, and forced vital capacity. PFF 40. Accordingly, none of the clinical studies disclosed in the '793 patent inform the POSA how to successfully practice the asserted methods. *Id*. The subjects in each study received one dose of inhaled treprostinil, after which their hemodynamics were monitored for no more than 3 hours. *Id*. The study populations were also comprised almost entirely of WHO Group 1 and 4 subjects, and the data is reported in aggregate. PFF 40. Thus, it would be mathematically impossible for the POSA to disaggregate the data and draw conclusions regarding potential

treatment effects in PH-ILD specifically. *Id*. Further, the POSA would know that the changes in hemodynamics reported in the '793 patent are not necessarily correlated with the functional benefits—e.g., changes in exercise capacity—recited in the Asserted Claims, further reducing the predictive value of the '793 patent. *Id*. The POSA would therefore understand that, at most, the '793 patent teaches that a *single administration* of treprostinil can improve *hemodynamic measurements* in PH patients without regard for safety or efficacy—a far cry from the Asserted Claims. *Id*.

The '793 patent also contains very limited disclosures regarding treprostinil DPI formulations. For example, the POSA would recognize that the '793 patent fails to disclose any data from subjects administered treprostinil using a DPI. PFF 41. The '793 patent also fails to identify any device or formulation with any specificity. *Id*. These omissions would be particularly significant to the POSA here, who is a clinician, not a formulator. *Id.* Thus, even if the '793 patent discloses that single doses of dry powder inhaled treprostinil can improve hemodynamics, it tells the POSA nothing about how to improve exercise capacity in PH-ILD patients. PFF 40.

Finally, Liquidia argues that UTC has "admitted" to the USPTO and FDA that the '793 patent covers improving exercise capacity in PH-ILD patients. Liq. Br. at 12. Not so. While UTC informed FDA that the '793 patent *covers* the use of Tyvaso in PH-ILD (DTX28.0006), UTC did not inform FDA that the '793 patent *discloses* improving exercise capacity in PH-ILD. Nor could UTC do so, as the '793 patent is silent on exercise capacity and instead claims improving hemodynamics independent of safety or efficacy. PFF 40; *United Therapeutics*, 624 F. Supp. 3d at 461-62. UTC similarly never told the USPTO that the '793 patent discloses improving exercise capacity in PH-ILD. *See* DTX7.0071-72 ("the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension."). Here again, Liquidia draws a false equivalence between methods of the '793 patent and the '327 patent. PFF 40.

3. Saggar 2014

Liquidia relies on Saggar 2014 to argue that the clinical endpoints required by claims 5, 6, and 9 would have been obvious. Liq. Br. at 17-20. The POSA would not make this logical leap because Saggar 2014 reports on *parenteral*—not inhaled—treprostinil and employs a study design that would not allow the POSA to draw any conclusions regarding potential treatment effects in PH-ILD. PFF 42. Saggar 2014 thus cannot render claims 5, 6, or 9 obvious.

Unreliable Study Design: Saggar 2014 is an uncontrolled, prospective study that evaluated the use of parenteral treprostinil in a small cohort of 15 patients "with PF … who had advanced PH." PFF 43. This study design would present several challenges to the POSA. First, the POSA would understand that any effects observed from parenteral administration of treprostinil could not be readily extrapolated to an inhaled dosage form, and Liquidia does not point to any method or technique that the POSA could employ to do so. PFF 42. Second, because the study lacked a control group, the POSA would understand that the data lacks predictive value, especially given the different route of administration. *Id*. Third, the majority of patients in the study received concurrent background therapies, further confounding whether any purported effects were due to treprostinil. PFF 43. Fourth, Saggar 2014 reports results on a population basis but contains insufficient data for the POSA to conclude that all the patients had PH-ILD. *Id*. The authors of Saggar 2014 freely acknowledged these limitations, stating that "the routine use of PH-targeted therapies in PF-PH *is not recommended*" and that their findings "are *only hypothesis generating* and require confirmation in a multi-center randomized study design." PFF 46.

NT-proBNP (Claim 5): The POSA would know that BNP is a distinct biomarker from NT-proBNP, and neither Saggar 2014 nor Liquidia provides any basis or correlation by which the POSA could reliably interconvert them, especially when changing from parenteral to inhaled administration. PFF 44. Saggar 2014's small, uncontrolled nature, discussed above, would further

enhance the unpredictability to the POSA. PFF 43.

Exacerbations of ILD (Claim 6): Saggar 2014 provides no data or analysis regarding ILD exacerbations. PFF 42. Liquidia instead points to the disclosure of improvements in *two different clinical endpoints*—6MWD and dyspnea—and argues that these improvements would translate to reduced ILD exacerbations. Liq. Br. at 19. However, Liquidia has again pointed to no reliable metric by which the POSA would be able to readily extrapolate between these endpoints, especially when changing from parenteral to inhaled administration.

FVC (Claim 9): FVC data reported in Saggar 2014 represents neither a statistically significant (p-value=0.687) nor clinically significant change, particularly in a small, 15-patient study. PFF 45. Indeed, the authors reported that patients' pulmonary function "*remained unaltered* during the study." DTX0010.0005 (emphasis added). These results would carry no weight with the POSA, especially when contrasted with the FVC decline observed in Faria-Urbina 2018, which actually employed inhaled treprostinil and had much lower p-values. PFF 37, 45; *supra* § VI.B.1.

C. Liquidia's asserted combinations fail to establish obviousness

Liquidia asserts that claims 1, 14, and 17 are obvious over the combination of Faria-Urbina 2018 and the '793 patent. Liq. Br. at 11-17. For claims 5, 6, and 9, Liquidia adds an additional reference, Saggar 2014. *Id.* at 17-20. These combinations fail to disclose the claimed invention, either alone or in combination, and Liquidia has failed to establish that the POSA would have a motivation to combine them with a reasonable expectation of success.

1. Claim 1 is not obvious

Claim 1 is not obvious over Faria-Urbina 2018 and the '793 patent. Liq. Br. at 11-15. Claim 1 covers, *inter alia*, the use of inhaled treprostinil to improve exercise capacity in PH-ILD patients. Liquidia's combination does not disclose every limitation of claim 1, and Liquidia fails to prove the POSA would have been motivated to combine these references or would have had a

reasonable expectation of success in doing so. Because all other Asserted Claims ultimately depend from claim 1, Liquidia's failure to prove that claim 1 is obvious means that *no* Asserted Claim is obvious. *See Comaper Corp. v. Antec, Inc.*, 596 F.3d 1343, 1354-55 (Fed. Cir. 2010).

a) Liquidia's references do not disclose the limitations of claim 1

Faria-Urbina 2018 and the '793 patent do not individually or collectively disclose the limitations of claim 1. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). **Faria-Urbina 2018** notably fails to disclose the preamble of claim 1, which requires that the claimed methods be performed with the intentional purpose or expectation of improving exercise capacity in PH-ILD patients. D.I. 155; *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003). Given the state of the art, that was not possible: there had been too many failed studies, and the data in Faria-Urbina 2018 is flawed and lacks predictive value. *Supra* §§ VI.A.1-A.2, VI.B.1. **The '793 patent** is silent on exercise capacity and fails to disclose other limitations of claim 1, including the limiting preamble. *Supra* § VI.B.2. The '793 patent concerns hemodynamics, and even those data are not specific to any patient type. *Supra* § VI.B.2. A minority of the patients were identified as having "pulmonary fibrosis," but there is no evidence that their PH was "due, at least in part" to that "pulmonary fibrosis," and there is no data regarding whether any patients in the study improved their exercise capacity. *Supra* § VI.B.2.

b) No motivation to combine

Liquidia's alleged motivation to combine is legally insufficient. Vague attorney argument that the two references are directed to "the same subject matter" as the asserted claims does not pass legal muster. Liq. Br. at 12-15; *see Securus Techs., Inc. v. Glob. Tel*Link Corp.*, 701 F. App'x 971, 977 (Fed. Cir. 2017). Further, these references do not actually disclose the "same subject matter" as claim 1. *Supra* §§ VI.B.1, VI.B.2. The '793 patent is about acute hemodynamics, and Faria-Urbina 2018 is a small retrospective chart review with no predictive value. *Supra* §§ VI.B.1,

VI.B.2; PFF 33-39. Nor were they designed to study the "same" patients—the claimed patients *must* have "pulmonary hypertension associated with interstitial lung disease." *Supra* §§ VI.B.1, VI.B.2. Regardless, stating that there is a "general motivation" is legally insufficient. *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014); *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008).

In April 2020, the use of PAH drugs—including inhaled treprostinil—in PH-ILD patients was highly controversial due to failed trials and a lack of data supporting efficacy. *Supra* § VI.A. Leading physicians and consensus treatment guidelines recommended *against* this practice, and the field was pessimistic that any PAH drug would ever be successful in PH-ILD. *Supra* § VI.A. Moreover, the POSA would *not* have viewed the data in Faria-Urbina 2018 and the '793 patent as predictive of treatment effects in PH-ILD patients, especially given the documented failure of pilot studies in this patient population. *Supra* §§ VI.A, VI.B.1, VI.B.2. There was nothing in the prior art to motivate the POSA to try inhaled treprostinil in PH-ILD, much less with the purpose of improving exercise capacity. *Supra* §§ VI.A, VI.B.1, VI.B.2; PFF 48. If anything, the prior art would have pushed the POSA in the opposite direction. *Supra* §§ VI.A, VI.B.1; *infra* § VI.D; *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343-45 (Fed. Cir. 2000) (defendant's motivation theory "has all the earmarks of somebody looking at this from hindsight"). Liquidia's reliance on statements made by UTC CEO Martine Rothblatt on a 2018 investor call (Liq. Br. at 1, 13) is similarly misplaced. Dr. Rothblatt is not a clinician, and her comments related to Group 3 PH generally, not PH-ILD specifically. PFF 68. Even assuming that the POSA would consider an investor call in their prescribing decisions (they would not), Dr. Rothblatt's comments would not prompt the POSA to take the risk of using inhaled treprostinil in PH-ILD. *Id.*

Finally, Liquidia's allegations of off-label use, however allegedly corroborated, cannot

establish a motivation to combine. Liq. Br. at 12-15.[5] Not only was much of this alleged use conducted behind closed doors—and thus unknown to the POSA—but the threshold requirement for a motivation is missing. *Infra* § VII; *supra* § VI.A; PFF 48, 63-64. Whether doctors were or were not experimenting with Tyvaso in PH-ILD patients, that has nothing to do with whether (or how) the POSA would combine the methods in Faria-Urbina 2018 with the methods in the '793 patent. *See Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1336-37 (Fed. Cir. 2010).

c) No reasonable expectation of success

Even if the POSA were motivated to combine Faria-Urbina 2018 with the '793 patent, the POSA would not have a reasonable expectation of success in achieving the methods of claim 1. As explained above, all of the previous failures of trials attempting to show safety and efficacy for PH-ILD using PAH therapies had failed and the field was characterized by pessimism. *Supra* § VI.A. Liquidia cannot pretend the POSA would have analyzed Faria-Urbina 2018 and the '793 patent in isolation. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Given this background as well as the clear defects of Faria-Urbina 2018 and the '793 patent, the POSA would need more than what these references disclosed to have a reasonable expectation of success. *Supra* §§ VI.A, VI.B.1, VI.B.2; PFF 27, 33-41, 49. The POSA would readily understand that the data Faria-Urbina 2018 reported was of far lower quality than the Hoeper pilot study that preceded the failed RISE-IIP trial, and there is nothing in the '793 patent or any other reference to fill that gap. *Supra* §§ VI.A, VI.B.1, VI.B.2; PFF 35, 40-41, 49. To the contrary, Faria-Urbina 2018 and the other prior art Liquidia cites emphasized the limited predictive value of small pilot studies and recognized that larger trials were needed to assess potential treatment effects. *Supra* §§ VI.A, VI.B.3; PFF 47.

[5] Liquidia also asserts that its allegations of off-label use are relevant to reasonable expectation of success; they are not for the same reasons discussed above with respect to motivation.

Claim 1 requires that the POSA administer inhaled treprostinil to a PH-ILD patient with the intent of improving their exercise capacity. D.I. 155. As discussed in detail above, there is nothing in either Faria-Urbina 2018 or the '793 patent that would give the POSA confidence that inhaled treprostinil would safely and effectively improve exercise capacity in PH-ILD patients. *Supra* §§ VI.B.1, VI.B.2; PFF 33-41, 49. The POSA would recognize that the clinical data reported in Faria-Urbina 2018 lacks predictive value due to serious flaws in the study's design, patient selection, and data quality. *Supra* §§ VI.A.1, VI.B.1. Further, even if the POSA took the data at face value, they would be concerned by the negative results reported for FVC and SpO_2, which suggest patient harm. *Supra* § VI.B.1; PFF 37, 49. Taken together, these clear problems would prevent the POSA from being able to draw any reasonable conclusions regarding potential treatment effects in PH-ILD. *Supra* §§ VI.A.1, VI.B.1; PFF 49. The '793 patent would not resolve the POSA's concerns because, as discussed above, it reports single-dose hemodynamic data from a heterogeneous population of PH patients. *Supra* §§ VI.A.1, VI.B.2; PFF 49, 51-52. The POSA could not draw any conclusions from this data regarding exercise capacity in PH-ILD patients.

Perhaps realizing its failure of proof, Liquidia points to legal authority stating that the standard to prove obviousness is different from (and lower than) that required to obtain FDA approval for a new medication. Liq. Br. at 13. UTC has never argued to the contrary. Obviousness, and by extension reasonable expectation of success, is a highly fact-intensive inquiry that can vary depending on the invention and the state of the art. *In re Ochiai*, 71 F.3d 1565, 1570 (Fed. Cir. 1995); *In re Entresto*, 125 F.4th 1090, 1100 (Fed. Cir. 2025); *Sanofi v. Glenmark Pharms. Inc., USA*, 204 F. Supp. 3d 665, 691-96 (D. Del. 2016). Here, the art was characterized by failure, controversy, and hopelessness. *Supra* § VI.A. A series of six failed clinical trials in PH-ILD, including the disastrous RISE-IIP study that published immediately before the priority date, meant that the field was outwardly skeptical of using PAH drugs in this indication. *Supra* § VI.A. Liquidia

insists that none of these past failures involved treprostinil (Liq. Br. at 14-15), but this is inconsistent with the prior art literature, which raised concerns about the use of PAH drugs *as a class*. *Supra* § VI.A. Indeed, these concerns made it very difficult to enroll patients in the INCREASE trial. PFF 55. Given all of the uncertainty in the field, the POSA would have needed to see more than flawed data from small, retrospective studies to have a reasonable expectation that inhaled treprostinil would improve exercise capacity in PH-ILD patients. *Supra* §§ VI.A, VI.B.3; PFF 27, 49. Liquidia attacks Dr. Nathan's opinion that the POSA would require a randomized, placebo-controlled trial as "contrary to law" (Liq. Br. at 13), but this mischaracterizes his testimony. Dr. Nathan made clear that while such a trial might not be required in all circumstances, the extreme uncertainty in the PH-ILD field and the low quality of existing data for treprostinil would increase the level of proof the POSA needed to see. PFF 49. Thus, Dr. Nathan's opinions—which account for the particular challenges faced by the POSA—are entirely consistent with governing precedent. *Ochiai*, 71 F.3d at 1570; *Sanofi*, 204 F. Supp. 3d at 696.

2. Claim 14 is not obvious

Liquidia's combination of Faria-Urbina 2018 and the '793 patent do not render claim 14 obvious. Liq. Br. at 15-17. Claim 14 depends from claim 1 and further requires the use of a dry powder inhaler (DPI). Liquidia argues that: (i) the POSA would arrive at this limitation based solely on claim 4 of the '793 patent and four sentences in that patent's specification; and (ii) UTC is "collaterally estopped" from arguing that a treprostinil DPI formulation is non-obvious. *Id.*; DFF 69; DTX0002 at 7:22-26, 7:42-54, 18:36-37. Both arguments fail because they rely on a fundamental misreading of the '793 patent and the impact it would have on the POSA.

a) Liquidia's obviousness theory lacks merit

Liquidia's hindsight-driven, patchwork obviousness theory for claim 14 requires the POSA to make a series of logical leaps that are entirely unmoored from their knowledge and experience.

According to Liquidia, the POSA would be motivated to start with Tyvaso solution, convert it into a novel DPI formulation, and expect the new DPI to safely and effectively improve exercise capacity in PH-ILD. Liq. Br. at 15-17. However, Liquidia has not proven by clear and convincing evidence that the POSA would perform any one of these steps, let alone all three.

No motivation to use Tyvaso: As discussed above with respect to claim 1, the POSA would not have been motivated to use inhaled treprostinil to improve exercise capacity in PH-ILD. *Supra* § VI.C.1. Liquidia relies on Faria-Urbina 2018 and post-critical date allegations of off-label use to assert a "motivation" to use inhaled treprostinil in PH-ILD, all of which reflects the use of *nebulized Tyvaso*. Liq. Br. at 11-13, 22-23. However, use of that nebulized formulation in PH-ILD was itself highly controversial and unsupported by reliable data, and the POSA would not be motivated to experiment with this risky and unproven treatment concept, much less have a reasonable expectation that it would work. *Supra* §§ VI.A; VI.B; VI.C.1, PFF 48-52.

No motivation to develop a novel DPI: Even if the POSA were motivated to try Tyvaso in PH-ILD, there would be no reason for the POSA to then substitute Tyvaso with an entirely new DPI formulation. This would be both incompatible with the POSA's training and inconsistent with Liquidia's proffered motivation to use treprostinil (i.e., pilot studies with *nebulized* Tyvaso). The use of *any* PAH drug in PH-ILD was controversial in April 2020, and the POSA—with two years of experience treating PH-ILD patients—would not assume the additional risk of administering an untested DPI formulation directly to the impaired lungs of this vulnerable population. *Supra* § VI.A; PFF 48, 51. No witness testified that they actually formulated and administered dry powder treprostinil to PH-ILD patients, and every physician Liquidia identifies as having used treprostinil off-label allegedly did so with *Tyvaso*, not a novel DPI. Liq. Br. at 11-13, 22-23. Liquidia similarly points to no clinical data in the prior art reflecting the use of a treprostinil DPI in PH-ILD or any other indication. If Dr. Channick, Dr. Hill, or any other of the expert clinicians Liquidia relies on

never tried to substitute Tyvaso for a novel DPI formulation, neither would the POSA.

In conclusory fashion, Liquidia suggests—in a single sentence (Liq. Br. at 17)—that the POSA would have "replace[d]" Tyvaso with a DPI *only* because it is "more convenient." This single sentence completely ignores the real-world risks of introducing an untested formulation and is insufficient to prove motivation by clear and convincing evidence to experiment with a vulnerable patient population when treatment via inhaled treprostinil was already controversial. Notably, Liquidia has provided no evidence suggesting that Tyvaso solution was inconvenient for patients. Instead, it improperly conjures motivation from thin air. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353-57 (Fed. Cir. 2013); *In re Omeprazole*, 536 F.3d 1361, 1380-81 (Fed. Cir. 2008); *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 935 (Fed. Cir. 2019).

No reasonable expectation of success: Even if the POSA were motivated to try a DPI formulation of treprostinil, they would not—and indeed could not—have a reasonable expectation of success in developing a formulation that would safely and effectively improve exercise capacity in PH-ILD patients. The POSA here is a PH-ILD clinician, not a pharmaceutical formulator, and thus could not develop *any* novel DPI formulation of treprostinil, let alone a formulation meeting the requirements of claim 14. PFF 49-52. Further, the '793 patent provides very limited disclosures with respect to a DPI—it does not disclose a particular formulation, a particular type of inhaler, or any clinical data from the use of a DPI. PFF 40-41. While this level of detail might have been enough for a trained formulator to generate a basic DPI formulation of treprostinil, there is no evidence suggesting that the POSA—a doctor with no formulation experience—would be able to do the same. PFF 40-41, 49-52. Liquidia asserts that UTC "admitted" in a prior litigation that "by 2006, it was well known how to develop dry powder formulations of treprostinil." Liq. Br. at 16. Even if this were true and applicable to the POSA *in this case* (it is not), it would only assist the POSA in *preparing* the DPI formulation, and would not provide any reasonable expectation that

the formulation would improve exercise capacity.

As discussed above, the '793 patent does not mention exercise capacity at all and is instead focused on *improving hemodynamics* in PH patients using *single doses* of inhaled treprostinil. *Supra* § VI.B.2. The POSA would recognize that this is very different from being able to improve *exercise capacity* in PH-ILD patients using the same type of *chronic dosing* employed by Tyvaso, and Liquidia points to nothing in the trial record that would allow the POSA to make this leap. *Id.* Thus, even assuming the POSA (or a formulator working at their direction) could use the '793 patent to develop a treprostinil DPI formulation that improved hemodynamics following a single dose, the POSA would not *assume* that this formulation would improve exercise capacity in PH-ILD patients as required by claim 14. PFF 40-41, 49-52. Indeed, in a field characterized by failure of new drug products, the POSA would have even less reason to expect that a new, untested DPI would be safe or effective. *Supra* §§ VI.A, VI.B.2; *Sanofi*, 204 F. Supp. 3d at 696. This uncertainty is reflected in the real-world experience of UTC and Liquidia when they each sought to develop DPI alternatives to Tyvaso—both companies had to combine the INCREASE data with additional studies showing that their dry powder formulation, and inhaler would safely deliver comparable amounts of treprostinil *per breath* as required by the claims. PFF 51. Because none of this data would have been available to the POSA in April 2020, *id.*, the POSA would need to first formulate a dry powder and then perform their own studies before they could even assess the performance of their DPI relative to Tyvaso. This is far from a reasonable expectation of success.

No alternatives to the '793 patent: Liquidia improperly invites the Court to rely on "other" evidence outside its obviousness combination, such as WO2019/237028 and the '507 patent. Liq. Br. at 15-16. Not only does this violate the Court's order limiting Liquidia's defenses (D.I. 317, 318), but there was no testimony at trial as to how the "other" references would apply to claim 14. *Supra* § IV.C. Liquidia cannot establish obviousness via "[u]nsubstantiated attorney

argument regarding the meaning of technical evidence." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005); *see also Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1151-52 (Fed. Cir. 2004) (refusing to credit attorney argument on reference not considered by party's expert); *Ferring Pharms. v. Par Pharm.*, 267 F. Supp. 3d 501, 505-06 (D. Del. 2017) (same); *In re Brimonidine Patent Litig.*, 666 F. Supp. 2d 429, 444 (D. Del. 2009) (same). The Court should not permit Liquidia to re-write its obviousness defenses post-trial. *See Endo Pharms. Inc. v. Amneal Pharms., LLC*, 224 F. Supp. 3d 368, 375 n.5 (D. Del. 2016).

b) Collateral estoppel does not apply

Liquidia argues in passing that "UTC is collaterally estopped from arguing that dry powder formulations of treprostinil with a suitable DPI were not obvious as of 2006." Liq. Br. at 15-16. This is incorrect. First, Liquidia has waived the ability to assert collateral estoppel because it raised the issue for the *first time* during post-trial briefing, and did not make this argument in its answer, invalidity contentions, expert reports, pre-trial filings, or trial presentation. In a prior litigation, this Court correctly held that Liquidia waived a collateral estoppel defense under similar circumstances. *UTC v. Liquidia*, No. 20-755-RGA, D.I. 410 (D. Del. May 12, 2022); *Id.*, D.I. 360 (D. Del. Mar. 18, 2022). The same result is required here. Second, Liquidia's argument fails on the merits because the '793 patent claims materially different subject matter than the '327 patent. *Supra* § VI.B.2. For example, the '793 patent involves different claim scope (single-dose hemodynamic improvements in PH generally), different clinical data in the specification (mixed populations, no exercise capacity), and a different POSA definition (includes pharmaceutical formulators) than the '327 patent. *Id.* These differences preclude collateral estoppel because they materially alter the question of invalidity. *See TQ Delta, LLC v. 2Wire, Inc.*, C.A. No. 13-1835-RGA, 2021 WL 2671296, at *5 (D. Del. June 29, 2021); *Joao Bock Transaction Sys. v. Jack Henry & Assocs.*, C.A. No. 12-1138-SLR, 2014 WL 2960363, at *10 n.34 (D. Del. June 30, 2014).

3. Claim 17 is not obvious

Liquidia's combination of Faria-Urbina 2018 and the '793 patent does not render claim 17 obvious. Liq. Br. at 15. As discussed above with respect to Claim 1, the POSA would not have been motivated to combine these references to improve exercise capacity in PH-ILD patients and would not have had a reasonable expectation in doing so. *Supra* § VI.C.1; PFF 48, 49. Claim 17 further requires an improvement in 6MWD by at least 10 m after 8 weeks of administration, which Liquidia attempts to meet by pointing to the 6MWD data in Faria-Urbina 2018. Liq. Br. at 15. However, not only is this data unreliable for all the reasons discussed above, but Faria-Urbina 2018 collected its data after *3 months* of administration, far longer than the 8 weeks required by claim 17. *Supra* § VI.B.1. There is also nothing in the prior art to give the POSA confidence that a patient's 6MWD could be improved by 10 m after only 8 weeks. *Supra* § VI.B.1; PFF 48-50. Further, the POSA would not, as Liquidia suggests, interpret claim 17 to encompass *any* period of administration longer than 8 weeks. Reading the claim term "after 8 weeks" in this way would both contradict the data in the specification (which reports discrete 6MWD data after 8 and 16 weeks), and render meaningless the "12 weeks" and "16 weeks" limitations in other claims that specify an 8-week timepoint, e.g., 5 and 9. '327 patent at Fig. 3, 4:42-46, 54:27-29, 54:42-45.

4. Claim 5 is not obvious

Liquidia's combination of Faria-Urbina and the '793 patent and Saggar 2014 does not render claim 5 obvious. Liq. Br. at 17-19. Claim 5 requires that a patient's plasma levels of NT-proBNP be reduced by at least 200 pg/ml after 8, 12, or 16 weeks of treatment, however none of the references Liquidia cites even mention NT-proBNP. *Supra* § VI.B; PFF 39, 40, 42, 48, 49. At best, Saggar 2014 mentions a related but different biomarker—BNP—but the paper only reports data from using parenteral treprostinil and provides way for the POSA could translate these results to NT-proBNP when using inhaled treprostinil. *Supra* § VI.B; PFF 48, 49. Neither Liquidia nor its

expert Dr. Channick is able to fill this gap, arguing only that BNP and NT-proBNP are "positively correlated." Liq. Br. at 17-19. But even if even if NT-proBNP and BNP are positively correlated when treprostinil is administered parenterally, there was no evidence at trial that this correlation would further translate when switching to *inhaled* administration of treprostinil. *Supra* § VI.B; PFF 48, 49. Liquidia points to Parikh 2016—which Dr. Channick did not address in his testimony on claim 5 (Tr. 478:13-482:20)—as purportedly confirming such a correlation in the inhaled context, but the data reported in Parikh 2016 was generated from a mixed population where just 6 of the 80 patients were characterized as having PH-ILD, and the reference says nothing about transitioning patients from parenteral to inhaled therapy. PFF 47. Liquidia's failure of proof here is even more pronounced because claim 5 requires not just a reduction of NT-proBNP but a reduction of *at least 200 pg/ml*. Even if the POSA took Saggar 2014's BNP results at face value, there is no evidence that the POSA would expect to produce the particular numerical improvement in NT-proBNP required by claim 5 when using inhaled treprostinil. *Supra* § VI.B; PFF 48, 49.

5. Claim 6 is not obvious

Liquidia's combination of Faria-Urbina 2018, the '793 patent, and Saggar 2014 does not render claim 6 obvious. Liq. Br. at 17-19. At the outset, claim 6 requires a statistically significant reduction of exacerbations of underlying ILD, but *none* of Liquidia's three references even discuss ILD exacerbations. *Supra* § VI.B; PFF 48, 49. Liquidia nonetheless asserts that the POSA would be able to infer a reduction in ILD exacerbations based on other clinical endpoints, i.e., 6MWD, dyspnea, and WHO functional class, reported in Saggar 2014 and Faria-Urbina 2018. Liq. Br. at 19. Liquidia's position is unsupported by evidence and instead relies on speculation and hindsight. This is especially true of Saggar 2014, which used parenteral treprostinil. PFF 48, 49. Further, Liquidia points to no clinical data or other rationale by which the POSA could reliably translate results in 6MWD, dypsnea, and functional class to create a statistically significant improvement

in ILD exacerbations, an entirely different endpoint. PFF 48, 49. Liquidia also ignores contrary data from Faria-Urbina 2018 showing that patients were hospitalized and exhibited reduced lung function (e.g., as measured by FVC). *Supra* § VI.B.1; PFF 48, 49. Far from suggesting a reduction in ILD exacerbations, these data would cause the POSA to worry that inhaled treprostinil could make exacerbations worse. *Id.* Finally Liquidia is incorrect that Dr. Nathan's testimony on this subject is irrelevant because it referred to "acute" exacerbations of ILD. DFF 98. The '327 patent consistently refers to ILD exacerbations as "acute" deteriorations in respiratory function, and the POSA would read claim 6 accordingly. JTX-0001.00033, 34, 36, 39.

6. Claim 9 is not obvious

Liquidia's combination of Faria-Urbina 2018, the '793 patent, and Saggar 2014 does not render claim 9 obvious. Liq. Br. at 17-20. Liquidia argues that claim 9's requirement for a statistically significant improvement in FVC is met by Saggar 2014, which used *parenteral treprostinil* to report a *non-significant* 1% improvement in percent predicted FVC. *Id.* Liquidia's argument fails for several reasons. Liq. Br. at 19-20. First, as discussed above, the POSA would have found the FVC results in Saggar 2014 to be unreliable and lacking in both clinical and statistical significance. *Supra* §§ VI.A.1, VI.B.3; PFF 48, 49. Liquidia points to post-priority testimony from Dr. Rajan Saggar (Liq. Br. at 20), but neither this nor any other evidence explains why the POSA would expect Saggar 2014's statistically insignificant results with parenteral treprostinil to translate to statistically significant results with inhaled treprostinil, as required by claim 9. Second, Liquidia ignores the contradictory FVC results reported in Faria-Urbina 2018, which actually used inhaled treprostinil and would have raised safety concerns for the POSA. *Supra* § VI.B.1; PFF 48, 49. Liquidia's failure to address these contrary results is textbook hindsight. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012). Third, Liquidia's attempt to draw parallels between the *prior art* data in Saggar 2014 and the *post*

art INCREASE data reported in the '327 patent is unsupported by law or fact. Liq. Br. at 19-20. Liquidia's overt reliance on the inventors' own data from the specification is both legally erroneous and, again, clear evidence of hindsight. *Zoltek Corp. v. United States*, 815 F.3d 1302, 1313 (Fed. Cir. 2016); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325-26 (Fed. Cir. 2000). Even if the POSA did consider this data, they would recognize that the statistically significant FVC improvement observed in INCREASE cannot be reliably compared to the non-significant FVC results from Saggar 2014. *Supra* § VI.B.3; PFF 4, 48, 49.

D. Objective indicia confirm the non-obviousness of the asserted claims

The non-obviousness of each Asserted Claim is confirmed by strong objective evidence. *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009); *Ortho-McNeil Pharm., Inc. v. Mylan Laby's., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Moreover, UTC's evidence of failure of others, teaching away, industry praise, and success is unrebutted.

Nexus: Each objective indicia discussed below is attributable to or a result of the claimed invention because the commercially successful features of Tyvaso and Yutrepia are coextensive with the Asserted Claims. *See Apple, Inc. v. Int'l Trade Comm'n*, 725 F.3d 1356, 1366 (Fed. Cir. 2013); *Fox Factory, Inc. v. SRAM, LLC*, 813 F. App'x 539, 542-43 (Fed. Cir. 2020). Examples 1 and 3 of the '327 patent disclose data from the INCREASE trial, which demonstrates the properties and features of the claimed invention. PFF 4-5. Based on this data, FDA approved Tyvaso, Tyvaso DPI, and Yutrepia for PH-ILD. PFF 3-5, 10. Nexus is plainly established here because each of these products is indicated and used for the same improvement claimed by the '327 patent—increased exercise capacity in PH-ILD. PFF 11-12, 53, 58. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1378 (Fed. Cir. 2000); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329-30 (Fed. Cir. 2016). Liquidia does not dispute this, and instead argues that UTC failed to prove nexus because Dr. Nathan did not compare the claims of the '327 patent to the closest prior art. Liq Op.

Br. at 20. This, however, is not the law. *See In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); *In re Merchant*, 575 F.2d 865, 869 n.8 (C.C.P.A. 1978). Liquidia further argues that the '793 patent should preclude nexus here because it is not materially different from the '327 patent and UTC has "admitted" that both patents cover "the same indication and dosing." Liq. Br. at 20-21. Not so. As discussed above, the '793 and '327 patents claim materially different inventions, and UTC has not made any "admissions" to the contrary. *Supra* §§ VI.B.2; VI.C.2. Just because both patents encompass the use of Tyvaso in PH-ILD does not mean that they cover the same *aspects* of that use (e.g., hemodynamics vs. exercise capacity). *Id.*

Unexpected results: The trial record makes clear that the results of the INCREASE trial were unexpected. Prior to INCREASE, numerous trials studying PAH drugs in PH-ILD had failed, creating significant doubts in the field. *Supra* § VI.A.1; PFF 26, 54; *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306-07 (Fed. Cir. 2015); *Leo Pharms. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). INCREASE was a "bold move" that broke this paradigm, showing that inhaled treprostinil could improve exercise capacity in PH-ILD patients. PFF 4, 29, 54, 57. INCREASE also showed significant—and surprising—improvements in key safety endpoints, such as FVC and ILD exacerbations. PFF 54. The FVC results were particularly notable because no drug had ever been shown to improve FVC in patients with ILD. PFF 54. Indeed, the Court heard substantial testimony that the results of INCREASE were surprising, unexpected, and groundbreaking. PFF 29, 54, 56. Liquidia offers a cursory analysis of unexpected results that ignores the weight of the evidence and rehashes Liquidia's flawed *prima facie* obviousness position. Liq. Br. at 21. But this cannot overcome the substantial, unrebutted evidence of unexpected results here. *Leo Pharm.*, 726 F.3d at 1358. Liquidia also accuses Dr. Nathan of not comparing INCREASE to "the closest prior art (e.g., *Faria Urbina*)," Liq. Br. at 21, but this is incorrect as a matter of both fact and law. *E.g.*, *Supra* § VI.B; PFF 33-46; *In re Grasselli*, 713 F.2d at 743.

Skepticism: Prior to INCREASE, the use of PAH drugs in PH-ILD was controversial, and there was a general sense of pessimism in the field. PFF 26, 29. This pessimism was driven by a series of failed clinical trials, several of which showed patient harm, and all of which failed to validate uncontrolled "pilot studies." PFF 26, 27. In short, the prevailing view as of April 2020 was that there was insufficient data to suggest that any PAH drug—including treprostinil—could safely and effectively treat PH-ILD, with many in the field questioning whether the use of these agents could be justified. PFF 26, 27, 30, 54, 66. This widespread skepticism was not merely academic and impacted the real-world prescribing practices of physicians. PFF 26, 29, 31, 55. Indeed, inventor Peter Smith had difficulty enrolling patients in the INCREASE study because physicians were worried about patient harm. PFF 55. Liquidia criticizes Dr. Nathan's testimony as merely reflecting "his own subjective beliefs—not that of the industry." Liq. Br. at 21. However, Dr. Nathan's testimony was offered from the perspective of the POSA and is corroborated by the medical literature, the testimony of Drs. Wertheim and Parikh, the testimony of the inventors, and the experience of Liquidia's own PH-ILD Advisory Board. PFF 26, 27, 31, 33, 38, 47, 55. Further, as discussed above, much of the testimony Liquidia cites as evidence of prior off-label use is both uncorroborated and contradicted by the physicians' own publications. That a few doctors of extraordinary skill may have used treprostinil experimentally in PH-ILD prior to April 2020 does negate the undisputed skepticism that existed in the field. Indeed, this is the very definition of a "controversy." Tr. 968:14-969:1.

Failure of Others: Before INCREASE, every drug that had been studied in PH-ILD had failed to show efficacy, with several drugs showing patient harm. *Supra* § VI.A.1; PFF 26. That the inventors of the '327 patent succeeded where so many others had failed is clear evidence that the Asserted Claims are non-obvious. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,* 676 F.3d 1063, 1081-82 (Fed. Cir. 2012).

Teaching Away: The repeated failure of PAH drugs in Group 3 PH and explicit warnings from Dr. Rubin, Dr. Nathan, Dr. Saggar, and others in the field would have discouraged the POSA from administering vasodilators like treprostinil to PH-ILD patients. *Supra* § VI.A; PFF 26. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Faria-Urbina 2018 reinforced these concerns, reporting declines in FVC and SpO_2 in patients administered inhaled treprostinil which would have told the POSA that the drug may not be safe for use in PH-ILD patients. *Supra* VI.B.1; PFF 37.

Long-Felt, Unmet Need: In April 2020, there were no approved therapies for PH-ILD despite many attempts, leaving this vulnerable patient population with limited treatment options. PFF 2, 26, 56. This is the very definition of a long-felt, unmet need. *See In re Cyclobenzaprine*, 676 F.3d at 1082. Tyvaso's approval for use in PH-ILD patients solved this unmet need, resulting in a paradigm shift in how doctors treat PH-ILD. PFF 56. At trial, Dr. Hill "thank[ed] God" that the results of INCREASE were positive, "because we now have an agent that is approved to treat PH-ILD." PFF 56. Liquidia argues that UTC "already admitted that the need was met by the '793 patent." Liq. Br. at 21. But the '793 patent claims hemodynamic changes, which do not predict the improvements in exercise capacity achieved by the Asserted Claims. *Supra* § VI.B.2; PFF 40.

Industry Praise: The approval of Tyvaso and Tyvaso DPI for PH-ILD was "well received" and met with "widespread enthusiasm." PFF 57. Doctors widely recognized the transformative impact of the INCREASE study and its results on the PH-ILD field. PFF 2, 56. In fact, *Liquidia CMO* Dr. Rajeev Saggar described UTC's work in PH-ILD as "nothing short of transformative." PFF 54, 57. This demonstrates that the claimed methods were anything but obvious.

Clinical & Commercial Success: Tyvaso and Tyvaso DPI have achieved substantial clinical and commercial success in PH-ILD. PFF 1-3, 56, 57. Dr. Nathan testified that he and many of his colleagues have used Tyvaso in "a lot of patients," since its approval for PH-ILD. PFF 57.

Copying: Yutrepia relies on and copies Tyvaso's INCREASE data and label to support its

PH-ILD indication and presents Yutrepia as clinically equivalent to Tyvaso in communications with the FDA, payors, doctors, and patients. PFF 3-6, 10-13, 58. Liquidia's decision to copy the claimed method without independent innovation supports the non-obviousness of the claimed invention. PFF 5, 10-16, 58. Liquidia argues that "Yutrepia is a different drug than Tyvaso" due to its dry powder formulation, Liq. Br. at 21, but this difference did not prevent Liquidia from relying on UTC's Tyvaso data to both obtain FDA approval for Yutrepia and to tell the world that the drugs perform equivalently in PH-ILD.

VII. THE CLAIMED METHODS WERE NOT THE SUBJECT OF A "PRIOR SALE"

Liquidia's "prior sale" defense is legally and factually defective. The on-sale bar "requires that (1) the invention be the subject of a commercial sale or offer for sale and (2) the invention be 'ready for patenting' at the time of the offer or sale." *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 996 (Fed. Cir. 2007). Liquidia alleges that third-party sales of Tyvaso for purported "off-label use" triggers the on-sale bar. Liq. Br. at 22-25. Liquidia is wrong for three independent reasons. First, Liquidia has not proven that "the invention" was ever on sale before the critical date because sales of Tyvaso (the *product*)—which is used with multiple methods—are not sales of the claimed *method of use*. This alone ends the inquiry. Second, it is undisputed that UTC did not sell or offer Tyvaso for sale to treat PH-ILD before the critical date, and allegations of third-party use of Tyvaso do not implicate the on-sale bar as a matter of law. Third, Liquidia has not proven that the claimed invention was ready for patenting prior to the critical date.

A. There is no evidence that the "claimed invention" was sold or offered for sale

Despite this Court's invitation to brief the law (Tr. 976:7-977:11), Liquidia declined to elucidate the circumstances under which a sale of a *product* constitutes an invalidating sale of a *method of use*. Instead, Liquidia completely ignores the Federal Circuit's foundational case on this issue, *BASF Corp. v. SNF Holding Co.*, 955 F.3d 958 (Fed. Cir. 2020), and asserts that "[t]he

claimed invention of the '327 patent was on sale under § 102(a) because Tyvaso was the subject of a sale to PH-ILD patients." Liq. Br. at 23; Tr. 994:9-995:5; D.I. 334-4 at ¶ 127. Liquidia's decision not to address *BASF*'s dispositive holding is telling.

As explained in detail below, Liquidia did not (and cannot) prove that the claimed method was ever put "on sale." Indeed, sales of Tyvaso cannot constitute sales of the claimed method because Tyvaso has more than one use—including treating PAH patients, which was Tyvaso's *only* approved use pre-critical date (April 2019). PFF 59; *BASF*, 955 F.3d at 970-71. Consistent with this, before the critical date, Tyvaso was prescribed and reimbursed for PAH patients, *not* PH-ILD patients, and Liquidia's tangled web of inferences are insufficient to prove otherwise. *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991). Finally, Liquidia has not shown inherent anticipation of the dependent claims by prior sale.

1. Sales of Tyvaso do not put the claimed method "on sale" under *BASF*

There was a single approved use for Tyvaso before the critical date: PAH. Liquidia admits "without question" that "PAH" is "not covered by the asserted claims of the '327 patent." Liq. Br. at 37. That ends the inquiry. Even if a Tyvaso sale had occurred for PH-ILD patients, it would not qualify as an invaliding sale under black letter Federal Circuit law because sale of a *product* cannot invalidate a *method claim* unless the product "embodies" the method and the two are "inseparable." Here—where it is undisputed that PAH was the ***only*** FDA-approved use—Liquidia cannot meet that exacting § 102 standard. PFF 59.

Sale of a product constitutes sale of a method *only* where the product necessarily "embodies essential features" of the method, i.e., the product is not "capable" of other uses. *BASF*, 955 F.3d at 970-71 (equipment did not "substantially embody the essential features" of claimed method because it "was capable of numerous [other] uses"). Rights in a patented method are only exhausted by a product if the product's "***only*** reasonable and intended use was to practice the

patent and" the product "embodie[s] essential features of the patented invention." *Quanta Comput., Inc. v. LG Elecs.*, 553 U.S. 617, 631 (2008) (internal brackets omitted, emphasis added).

Because Liquidia cannot show a sale of the claimed *method* under *BASF*, it has concocted a misguided theory based on a strained reading of *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 424 F.3d 1276 (Fed. Cir. 2005) and *Petrolite Corp. v. Baker Hughes Inc.*, 96 F.3d 1423 (Fed. Cir. 1996). According to Liquidia, a "method claim may be 'on-sale' where a product is sold *and used* to perform the claimed method." Liq. Br. at 25 (emphasis added). As an initial matter, Liquidia has waived reliance on public use. Even so, Liquidia's argument has no basis in law. *BASF* expressly rejected the argument that the on-sale bar applies to the "conveyance of a product that enables the recipient to perform a later-claimed process." 955 F.3d at 969; *id.* at 970 ("The on-sale bar does not turn on … whether the licensee is capable of performing the licensed process."). *Enzo* and *Petrolite* are not at odds with *BASF*, which Liquidia never addresses.

Enzo does not help Liquidia. In *Enzo*, the patent at issue was directed to "nucleic acid probes that selectively hybridize with the bacteria that cause gonorrhea" *and* "methods for using those probes to detect the bacteria." 424 F.3d at 1278. Notably, the method claims identified the composition of the nucleic acid probe—not the method itself—as the "improvement" over the prior art (i.e., drafted in Jepson format). *Id.* at 1279. The court concluded that the patentee's sale of the probe invalidated the composition *and* method claims because, "carrying out such a hybridization assay is ***inseparable*** from the compositions themselves." *Id.* at 1285 (emphasis added). This reasoning aligns with *BASF* and patent exhaustion doctrine, which asks whether a product's "***only*** reasonable and intended use [is] to practice the patent[ed method]." *Quanta*, 553 U.S. at 631 (emphasis added). As further explained below, and as Liquidia admits, it is "without question" that Tyvaso is not inseparable from the claimed method. Liq. Br. at 37.

Petrolite fares no better. The only issue on appeal was experimental use because the patentee conceded that the claimed hydrogen scavenging method was "publicly used and sold prior to the critical date[,]" so the court did not address whether the product was "inseparable" from the claimed method. *Petrolite*, 96 F.3d at 1426. In any case, *Petrolite* was decided before *BASF* but is nonetheless consistent with its holding because Petrolite's chemical product was specifically developed for use as a hydrogen sulfide scavenger (*id.* at 1424-25) and no other known uses are detailed. Thus, its "only … use was to practice the patent[ed method] and ... [the product] embodied essential features of the patented invention." *Quanta*, 553 U.S. at 631; *cf. BASF*, 955 F.3d at 969-70; *Poly-Am. v. GSE Lining Tech.*, 383 F.3d 1303, 1308-09 (Fed. Cir. 2004) (product sale that *could* be used to practice claimed method did not bar patenting). *BASF* forecloses Liquidia's "Tyvaso" on-sale theory. *BASF*, 955 F.3d at 970-71.

2. Tyvaso was sold for treating PAH, not performing the claimed method

Liquidia has not established by clear and convincing evidence that sales of Tyvaso put the claimed method on sale. Liquidia's evidence boils down to purported off-label Tyvaso use. Liq. Br. at 23 ("This consistent and widespread off-label *use*—which started well before April 2019—demonstrates that Tyvaso was being *used* to treat PH-ILD patients in a manner that satisfies the claimed limitations." (emphasis added)); *id.* at 25 (concluding that "[b]ecause the prescriptions identified the patients as having PH-ILD, the sales were specifically for the treatment of PH-ILD."). Liquidia's waiver of its prior "use" defense and *BASF* bars this theory. Nonetheless, prior to approval, there were no "sales" of Tyvaso with labels, packaging, or instructions concerning the method of using Tyvaso to increase exercise capacity in PH-ILD patients. *See, e.g.*, § VII.B; PFF 69. Even if PAH sales were used with PH-ILD patients, expert physicians "couldn't know" if they were "treating" PH-ILD pre-critical date and understood it was "experimental." PFF 69; Tr. 353:21-355:1.

Different patient population: A sale of Tyvaso—indicated for PAH and purportedly prescribed for PH-ILD patients—would not put the claimed method "on sale." Pre-critical date, the Tyvaso label was limited to Group 1 PAH and expressly warned about risk in using with patients having significant "underlying lung disease." PFF 59. Even assuming conclusory post-hoc testimony were sufficient—it is not—an insurance company covering Tyvaso for patients with PH-ILD is not tantamount to a sale of the claimed method because (1) no method was ever sold and (2) the drug product sold was explicitly limited by its label, packaging, and warnings.

Different dosing: Pre-critical date, the Tyvaso label provided a different dosing schedule than the now-claimed methods. The label provided for dosing as low as 6 mcg up to only 54 mcg, while the method of claim 1 requires "at least 15 micrograms up to a maximum tolerated dose." PFF 60; JTX-0001.00050 (claim 1). In the claimed method, the "maximum tolerated dose" "is determined by titrating the dose upwards until the maximum tolerated dose for the individual subject is determined," such that there is no 54 mcg limit. Thus, *even assuming* a "sale" of Tyvaso for a PH-ILD patient, that alleged "sale" would not necessarily practice the claimed method because the label itself instructs different doses. PFF 60; *see also BASF*, 955 F.3d at 970-71.

Purported Evidence of Claimed Improvements Do Not Demonstrate Sale: Liquidia's assertion that doctors saw improvements in exercise capacity, 6MWD, and NT-proBNP levels (Liq. Br. at 22), is based on testimony that is entirely subjective or otherwise founded on unreliable data. PFF 38, 66. For example, Dr. Channick's testimony was conclusory, claiming he knew there were improvements based on whether patients were "able to do more." PFF 66. This is at best a subjective anecdotal report and fails to demonstrate that administration of treprostinil caused an improvement in 6MWD, particularly given the possibility of a placebo effect. And as described more fully in § VI above, Faria-Urbina 2018 and Parikh do not demonstrate "that Tyvaso was being used to treat PH-ILD patients in a manner that satisfies the claimed limitation" (Liq. Br. at

22-23) much less evidence an offer or sale. PFF 67; PFF 33-39.

No Evidence the Claimed Method was Sold. Liquidia has not established that the claimed invention was sold. Instead, Liquidia's entire prior sale case assumes there was a sale for PH-ILD because some doctors claim that payment for treatment was initially denied, but later approved. *See* Liq. Br. 23 (arguing "[t]he fact that insurers denied coverage establishes that the prescriptions were not for PAH—otherwise they would have been approved," *but also claiming* "the fact that doctors ultimately secured insurance coverage is direct evidence that there was a commercial sale of Tyvaso for PH-ILD patients"). This speculative conclusion does not follow. Rather, the evidence supports the conclusion that any approval was due to the insurer concluding this expensive treatment was justified based on PAH—not PH-ILD. This is a far cry from clear and convincing evidence that any alleged sale was for patients with "pulmonary hypertension due, at least in part, to a patient's interstitial lung disease" as the claims require. D.I. 393. And it is undisputed that many patients who present with ILD ***do not have PH***. PFF 61.

There is no corroboration for prescriptions identifying patients as having PH-ILD. In fact, the undisputed evidence offered at trial demonstrated that patients that were prescribed Tyvaso pre-critical date had at least some "PAH" in their diagnosis. PFF 61. Dr. Hill confirmed as much, testifying that he was "not aware" of Drs. Waxman, Rajan Saggar, Tapson, or Channick "using [Tyvaso] where there [wa]s no PAH involved." *Id.* And, as the trial testimony demonstrated, physicians prescribing Tyvaso before April 2019 told insurance companies that the prescription was for "PAH." PFF 62. For example, Dr. Wertheim testified he had to "assert on the form and in my associated medical documentation that patients had PAH." *Id.* Dr. Nathan testified that he followed a similar process. *Id.* Even Liquidia's witnesses described representing to insurance companies "that the patient had precapillary PH, which is what you see in Group 1," and that the prescription "was for a PAH component of their disease that was out of proportion." *Id.*

Liquidia has not explained how a sale for Group 1 PAH constituted a sale to improve exercise capacity in a patient with "pulmonary hypertension due, at least in part, to a patient's interstitial lung disease." PFF 61. Nor has Liquidia offered any documentation from any prescribing physician, such as the appeal letters Dr. Hill purportedly submitted to insurers, or any corroborating evidence of a physician "convincing" an insurer to approve a prescription for a PH-ILD patient. PFF 63. Liquidia's proof is especially weak because it depends on the uncorroborated testimony of Dr. Hill, who was repeatedly impeached at trial, and thus, is not credible on this point. PFF 63, 70. Regardless, even if a prescription for Tyvaso was covered by insurance, that does not establish that the prescription was for a patient with "pulmonary hypertension due, at least in part, to a patient's interstitial lung disease" as required by claim 1. D.I. 393. In fact, Dr. Hill testified that "the patient had precapillary PH which you see in Group 1 [PAH]" "[a]nd "the patient had interstitial lung disease." Tr. 650:21-651:16; PFF 62. Dr. Hill testified "that, *to me*, is PH-ILD." *Id.* (emphasis added). "Hill's 'concomitant' definition is not the claimed 'pulmonary hypertension associated with interstitial lung disease.'" D.I. 393 at 9 ("I reject Defendant's construction that 'associated with' simply means 'and.'"). Notably, Liquidia admits that Group 1 PAH is "an indication that, without question, is not covered by the asserted claims of the '327 patent[.]" Liq. Br. at 37. Thus, Liquidia has not proven any prescriptions were ever written for PH-ILD pre-critical date.

Earnings Call Does Not Evidence Any Invalidating Sale: Finally, Dr. Rothblatt's statements do not "confirm" sales of the claimed method or even Tyvaso to PH-ILD patients. Liq. Br. at 23-24. First, there is no evidence in Dr. Rothblatt's statements to support that any claimed method was on sale or offered for sale. PFF 68; *supra* § VI.C.1.b. Second, Dr. Rothblatt's statements refer generally to "some WHO Group III patients," which includes PH-COPD patients. PFF 68. This is particularly relevant since her statement was made less than a week before the

PERFECT study in PH-COPD patients began. *Id*. Finally, Mr. Bunce confirmed that UTC was not "promoting or pushing pre-approval promotion for Tyvaso in Group 3" because "[a]s a company, we can't promote pre-approval promotion, so she did not, but as a company, we cannot." PFF 69. Indeed, even ***after*** the INCREASE Study, Liquidia's own advisory board "members said they were not aware of significant pre-approval prescribing of TYVASO® (treprostinil) in Group 3 PAH patients with ILD." *Id.* Liquidia has failed to prove that any sale of the invention took place at all. *See Intel*, 946 F.2d at 830 (challenger's proof "that … offers or sales may have been 'likely'" failed to meet clear-and-convincing evidence burden on prior sale).

Because the claimed method was never sold, Tyvaso was always prescribed and reimbursed for patients with PAH—which are "not covered by the asserted claims of the '327 patent" (Liq. Br. at 37)—and the Tyvaso label describes a different patient population and dosing, the claimed methods for treating PH-ILD were not sold prior to the critical date.

3. No inherent anticipation of dependent claims by prior sale

Liquidia also has not shown that any alleged sale of Tyvaso inherently anticipates any dependent claim. *See infra* § VIII. It is undisputed that no pre-critical date documentation exists proving that a method of treating PH-ILD patients was capable of a 200 pg/ml reduction in NT-proBNP (claim 5), a statistically significant reduction in exacerbations of ILD (claim 6), or a statistically significant improvement in FVC (claim 9). Liquidia instead argues that the claims are inherent in administering Tyvaso—but fails to account for differences between the 2009 Tyvaso label method and the claimed methods. This alone forecloses inherency. *Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, 2022 WL 3225381, at *6 (D. Del. Aug. 10, 2022), *aff'd*, 98 F.4th 1056 (Fed. Cir. 2024). Further, Liquidia has no evidence that these dependent claim limitations ever occurred or are *necessary and inevitable* consequences of administering Tyvaso (*see infra* § VIII). And it concedes that not virtually all patients would see such improvement. PFF 76.

Liquidia's inherency argument also fails because Liquidia simultaneously argues that Faria-Urbina 2018 is the claimed invention (Liq. Br. at 28) *and* that the claimed treatment effects are inherent, despite Faria-Urbina 2018 reporting *reductions*, not improvements, in FVC. PFF 37. Further, Liquidia ignores that dependent claims 5, 9, and 17 each require the claimed administration to continue for at least "8 weeks" to meet the claim, but Tyvaso comes in 28-day kits (less than 8-weeks). PFF 65. And there is no evidence that patients practicing the method necessarily and inevitably fill a second Tyvaso prescription, or that the claimed treatment effect was met. *See id.* Further, as Dr. Hill admitted, no physician offered any testimony regarding increases in six-minute walk distance after 8 weeks. PFF 66.

B. Alleged third-party sales do not trigger the on-sale bar

It is undisputed that UTC did not sell Tyvaso for PH-ILD pre-critical date. PFF 69. The only alleged "sales" are those purportedly among unknown third parties. Liq. Br. at 23-25. Allegations of "likely" sales are not sufficient to meet Liquidia's exacting burden. *Intel*, 946 F.2d at 830. Regardless, Liquidia's third-party on-sale defense fails as a matter of law.

First, a third party's alleged use of a claimed method "cannot implicate the on-sale bar as a matter of law" because "[s]ales or offers made by others and disclosing the claimed invention implicate the 'public use' provision of 35 U.S.C. § 102(b)." *Medtronic Inc. v. Edwards Lifesciences Corp.*, 2013 WL 12113417, at *22 (C.D. Cal. Sept. 17, 2013) (alteration original, emphasis omitted) (quoting *ResQNet.com, Inc. v. Lansa, Inc.*, 594 F.3d 860, 866 (Fed. Cir. 2010)). The court in *Schlumberger Tech. Corp. v. BICO Drilling Tools, Inc.* likewise held that third party sales "should be analyzed under the public use prong," not the prior sale prong, of § 102. 2019 WL 2450948, at *6 (S.D. Tex. June 12, 2019) (citing *ResQNet.com* and *In re Caveney*, 761 F.2d 671 & n.5 (Fed. Cir. 1985)). Liquidia's cases are not to the contrary. In *Special Devices, Inc. v. OEA, Inc.*, 270 F.3d 1353, 1355 (Fed. Cir. 2001), the patentee itself disclosed the invention and

made a commercial offer to buy it from a supplier, and in *In re Epstein*, 32 F.3d 1559, 1566-67 (Fed. Cir. 1994), the Court analyzed the public use and on-sale bars together and is thus consistent with *ResQNet*. Here, Liquidia waived the "public use" defense (D.I. 346 at 2), so it attempts to convert alleged third-party use into invalidating "sales," but that is foreclosed by law.

Second, it is well established that "[t]here is no reason or statutory basis … on which [third parties'] secret commercialization of a process, if established, could be held a bar to the grant of a patent to [the patent owner] on that process." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983). Liquidia cites *Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 586 U.S. 123, 130 (2019) to say that secret sales are invalidating (Liq. Br. at 25), but *Helsinn* only considered sales *by the patentee* and merely confirmed that the AIA had not displaced pre-AIA prior sale caselaw. *Helsinn*, 586 U.S. at 129-32. In contrast, the only allegations made by Liquidia are non-qualifying secret third-party sales—without any documentary corroboration. PFF 63-64.

In fact, Liquidia failed to present evidence of a single pre-priority public sale. Liquidia's expert, Dr. Hill, acknowledged that prescriptions are confidential under HIPAA. PFF 64. Dr. Hill never provided any documents evincing his alleged prior use of Tyvaso in PH-ILD patients. PFF 63. Indeed, to the extent any Tyvaso sales were allegedly for PH-ILD, that was secret even to the alleged seller (specialty pharmacies) and (the alleged buyer) payors, as doctors testified that they prescribed Tyvaso for PAH "out of proportion" to lung disease, not for "PH-ILD." *See, e.g.*, PFF 61-62. Such secret "sales" do not qualify under § 102. *W.L. Gore*, 721 F.2d at 1548 (third-party sale of product did not invalidate claim for method of making product because public could not learn the claimed process by examining the product); *TorPharm, Inc. v. Ranbaxy Pharms.*, 336 F.3d 1322, 1327 (Fed. Cir. 2003) ("[I]f the product were sold by one other than the patentee, and the process of making remained unknown, then sale of the product would not pose a statutory bar to a claim on the process."). Nor did Dr. Rothblatt somehow render otherwise-unknown-secret

sales public. Her comments were not specific to "PH-ILD," or any individual sale, and disclosed nothing about what triggered any prescription, much less the dosing or method of use prescribed. PFF 68. Liquidia cannot carry its burden under the exacting § 102 anticipation standard with generalized allegations of secret third-party sales.

C. The claimed methods were not ready for patenting

Liquidia's prior sale theory independently fails because the claimed method was not "ready for patenting." As an initial matter, Liquidia titles § V.B to include claims "1, 5, 6, 9, and 17," but fails to address claims 5, 6, and 9. Liq. Br. at 25-27. Those arguments are now waived. Liquidia admits, as it must, that ready for patenting "requires" "possession" of the claimed methods and that inventions are "shown to work." *Id*. at 25. Prior to INCREASE, none of the claims were. [6]

1. The claims were not ready for patenting as "reduced to practice"

"To demonstrate reduction to practice, a party must prove that the inventor (1) 'constructed an embodiment or performed a process that met all the limitations' and (2) '*determined* that the invention *would work* for *its intended purpose*.'" *In re Omeprazole Pat. Litig*., 536 F.3d 1361, 1373 (Fed. Cir. 2008) (emphasis added). Largely ignoring the second prong—the inventor (wholly missing from Liquidia's analysis) having determined that the claimed methods "would work"—Liquidia argues only that "real world treatment" demonstrates reduction to practice. Liq. Br. at 26. But anecdotal accounts do not demonstrate a treatment effect. PFF 66; PFF 27, 33; *Omeprazole*, 536 F.3d at 1373-74. In such an unpredictable field, testing is necessary to show the claimed methods are safe and effective where otherwise "the inventors believed only that the formulation '*might*'" work for its intended purpose. *Omeprazole*, 536 F.3d at 1373. Like in *Omeprazole*, "[t]he existence of the formulation … does not establish that the [UTC] scientists had determined that the invention would work for its intended purpose." *Id.* at 1374. And indeed, they had not—the

[6]INCREASE was completed and its results unblinded in 2020, after the critical date. PFF 22, 54.

INCREASE trial was necessary, as recognized both by the inventors *and* physicians purportedly prescribing off-label. PFF 26-27, 54, 56. Liquidia's § 112 challenge to claim 9 is illustrative: claim 9 is supported in part by the INCREASE trial's FVC results disclosed in the specification—if Liquidia contends claim 9 lacks § 112 support now, it defies logic that it could have been ready for patenting *prior* to those INCREASE results.

Testing was particularly important here given (1) the unpredictability in treating the vulnerable patient population and (2) widespread industry belief at the time—including from leaders in the field—that using Tyvaso in this patient population risked harming patients. PFF 26-27, 49, 54; *see Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1323 (Fed. Cir. 2019). The controversial nature of the claimed methods are in stark contrast to Liquidia's cases. In *Minerva Surgical, Inc. v. Hologic, Inc.*, the inventor "testified that the disclosed versions of the [patented] device were nearly 'perfect.'" 59 F.4th 1371, 1381 (Fed. Cir. 2023). Similarly, in *Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, there was "overwhelming" pre-critical date evidence establishing efficacy including the patentee's public statements that a Phase II trial had already "demonstrated the efficacy." 855 F.3d 1356, 1373-74 (Fed. Cir. 2017). Liquidia's terse reduction to practice argument fails to establish that the inventors determined the claimed methods "would work" for their intended purposes prior to unblinding the INCREASE trial results. Tr. 875:19-882:5.

2. The claims were not ready for patenting by enabling disclosure

Liquidia argues that Dr. Hill believes Faria-Urbina 2018 would enable the POSA to practice claims 1 and 17. Liq. Br. at 26. This is despite Dr. Hill's attempt to walk back at trial his prior testimony that the reference "does not encompass a method of improving exercise capacity through the use or administration of inhaled treprostinil to treat PH-ILD." PFF 70. Dr. Hill's prior testimony cannot be reconciled with Liquidia's current position. And Dr. Hill's contrary position at trial cannot be reconciled with the limiting preamble of claim 1, which requires performing the

method of treatment with the knowledge that it is in fact a "method of improving exercise capacity." *See Eli Lilly*, 8 F.4th at 1341-42. Indeed, as discussed above, leaders in the field were discouraging use of Tyvaso in PH-ILD patients due to risk of harm, and the inventors—again missing from Liquidia's analysis—were similarly not convinced the invention would work until after the INCREASE trial was unblinded. PFF 54.

Beyond the factual shortcomings of its enablement argument, Liquidia ignores that "when development and verification are needed in order to prepare a patent application that complies with § 112, the invention is not yet ready for patenting." *Space Systems/Loral, Inc. v. Lockheed Martin Corp.*, 271 F.3d 1076, 1080-81 (Fed. Cir. 2001) (reversing on-sale bar invalidity where "the inventor himself was uncertain whether [the invention] could be made to work"). If the POSA would not "accept without question statements as to the effects of the claimed drug products and no evidence has been presented to demonstrate…those effects, an applicant…cannot establish enablement." *Bial-Portela & CA. S.A. v. Alkem Labs. Ltd.*, C.A. No. 18-304-CFC-CJB, 2022 WL 4244989, at *26 (D. Del. Sept. 15, 2022).

Faria-Urbina 2018's uncontrolled retrospective report with a small, systematically-biased sample was insufficient to demonstrate that inhaled treprostinil increases exercise capacity in patients with PH due at least in part to ILD. *Supra* § VI.B.1; PFF 33-39; *Petito v. Puritan's Pride, Inc.*, 35 F. Supp. 3d 494, 503, 504 & n.8 (S.D.N.Y. 2014) (no enablement where efficacy evidence consisted of three patients because "the sample size [was] so small, there [was] no control group[,] and the description [was] so sparse (*e.g.*, as to dosages, concentrations, frequency, other medications taken, and, most importantly, as to the number of patients who were treated … but *whose symptoms did not improve*)") (emphasis added). Liquidia fails to identify an enabling disclosure establishing the invention was ready for patenting. Tr. 875:19-882:5.

3. Liquidia's "hypothesis generating" argument is irrelevant

Liquidia's final argument focuses vaguely on the notion of "hypothesis generating" data but fails to cite any legal authority. Liq. Br. at 27. Worse, it simply assumes the conclusion, arguing that "'hypothesis generating' results means that it yielded positive results"—the opposite is true, i.e., the results are only "hypothesis generating" because the POSA *cannot yet determine* whether they are in fact "positive results." Liquidia alleges Faria-Urbina 2018 "la[id] the foundation for further research" (Liq. Br. at 27), but at best, Faria-Urbina 2018, "expresses hope that [inhaled treprostinil] could have therapeutic effects" in Group 3 PH patients, which is insufficient for ready for patenting. *CreAgri, Inc. v. Pinnaclife, Inc.*, 2013 WL 6673676, at *16-18 (N.D. Cal. Dec. 18, 2013), *aff'd*, 579 F. App'x 1003 (Fed. Cir. 2014). "The fact that a concept is eventually shown to be workable does not retrospectively convert the concept into one that was 'ready for patenting' at the time of conception." *Space*, 271 F.3d at 1080.

Finally, Dr. Nathan did not characterize the INCREASE FVC results as "hypothesis generating" with respect to the *claimed methods*. Instead, he referred to the surprising FVC results' effect on our understanding of fibrosis without regard to PH. PFF 79. There is no inconsistency between seeking the '327 patent only after unblinding the groundbreaking INCREASE trial that established the claimed methods work, and acknowledging that its data generated *further* hypotheses related to the use of treprostinil in patients with ILD but *without* PH.

VIII. THE 2017 STUDY DESCRIPTION DOES NOT INHERENTLY ANTICIPATE

The "2017 Study Description" (DTX0008) fails to explicitly or inherently disclose all the limitations of any claim of the '327 patent. It is not INCREASE, was never performed, and the results were unknown and unpredictable. Liquidia has not met its burden.

A. The 2017 Study Description does not disclose or necessarily and inevitably lead to any of the claimed methods or treatment effects

The 2017 Study Description describes, at a high level, a proposed trial that was not

conducted. DTX0008; PFF 71. It has no results and fails to disclose the claimed effects and therefore does not expressly anticipate. *Id.* Liquidia's pivot to inherency likewise fails.

Inherency "may not be established by probabilities or possibilities" and "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Rapoport v. Dement*, 254 F.3d 1053, 1063 (Fed. Cir. 2001). Proving inherency is not an issue of 'close enough.' Rather, "[e]xperiments that do not follow the prior art procedure alleged to inherently anticipate cannot show inherent anticipation." *Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, 2022 WL 3225381, at *6 (D. Del. Aug. 10, 2022), *aff'd*, 98 F.4th 1056 (Fed. Cir. 2024).

INCREASE did not follow the asserted prior art procedures in the 2017 Study Description. It followed a different, longer, and more detailed protocol with a different dosing method and different patient population. PFF 71-76. In the 2017 Study Description, dosing starts at 1 breath with 6 µg of treprostinil delivered per breath, while INCREASE started dosing at 3 breaths of Tyvaso, and claim 1 of the '327 patent requires at least 15 µg of treprostinil. PFF 72-73. The inclusion and exclusion criteria also differ, including for parameters such as PVR, mPAP, PCWP, baseline diffusing capacity of the lungs for carbon dioxide, and FVC. PFF 74-75. Thus, the results of INCREASE cannot be used to show inherent anticipation. *Id.*; *In re Armodafinil Pat. Litig. Inc.*, 939 F. Supp. 2d 456, 478 (D. Del. 2013).

Liquidia asserts that UTC offered no evidence that the differences in dosing inclusion and exclusion parameters would have impacted the outcome of the INCREASE study and that "[e]ither way, the entire population from the 2017 [Study Description] is included in INCREASE." Liq. Br. at 32-33. Liquidia's characterization of the differences as "small" is both incorrect and not relevant. INCREASE indisputably "[did] not follow the prior art procedure," the differences could yield trial results that do not meet all limitations of the asserted claims (PFF 75), and therefore INCREASE "cannot show inherent anticipation." *Salix Pharms.*, 2022 WL 3225381, at *6. As to

magnitude, the burden for invalidity remains upon Liquidia, so it must prove—by clear and convincing evidence—that these differences could not cause the results of the hypothetical, not-run 2017 Study Description trial to fall outside the claims. It has not done so; these differences would impact the results.

Dosing: Dr. Nathan offered unrebutted testimony that the lower, one-breath starting dose makes it impossible to predict whether the method in the 2017 Study Description would have caused an increase in exercise capacity. PFF 71-73; *Salix*, 2022 WL 3225381, at *6. Liquidia's attempts to import the dosing of the 2009 Tyvaso label that doctors supposedly "knew" (Liq. Br. at 33) to modify the one-breath starting dose of the 2017 Study Description to change to a three-breath dose are flawed. First, as Dr. Nathan explained, the 2017 Study Description "is a new protocol. It's not necessarily following the label of the 2009 label." Tr. 919:23-920:2. Second, anticipation considers the reference itself; "[w]hat [the] POSA would have been able to practice based on [the 2017 Study Description]'s disclosure is not at issue." *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 845 (Fed. Cir. 2020). The 2017 Study Description does not disclose the same dosing as in INCREASE. *Rapoport*, 254 F.3d at 1063. Dr. Channick agreed, testifying that there are differing target and maximum doses. PFF 73. The 2017 Study Description's range of doses also does not disclose the specific "at least 15 μg" dosing recited by the claims. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

Patient population: Dr. Nathan made clear that by using the 2017 Study Description patient population, "[y]ou would have ended up with a very different result." PFF 71-76. Likewise, Dr. Channick testified that "I don't think anybody can say that" the 2017 Study Description patient population "would have exactly the same results" as observed in INCREASE. And, in fact, he admitted that he "can't predict the results" of administering inhaled treprostinil to the 2017 Study Description patient population. PFF 71.

For example, patients with PVR of 3-4 Wood Units were included in INCREASE but would have been excluded from the 2017 Study Description patient population. PFF 74-75. Dr. Nathan also testified that these PVR 3-4 patients powered the reduction of acute exacerbations observed in INCREASE. PFF 75. This unrebutted testimony based on real INCREASE data shows that Dr. Channick's speculation regarding what might have happened had the 2017 Study Description been performed is unreliable. PFF 71, 75-76. Using the 2017 Study Description patient population would have resulted in fewer if any endpoints being met, demonstrating that the asserted claims would not necessarily and inevitably be met if the 2017 Study Description were performed. PFF 74-76. The 2017 Study Description also lacks the FVC requirement present in the INCREASE study, so if carried out it would have *included* certain connective tissue disease patients who would have been *excluded* from the INCREASE study. PFF 74. Thus, Liquidia's theory that the 2017 Study Description is a predictive subset of INCREASE's population is wrong. *Glaxo Grp. Ltd. v. Kali Labs., Inc.*, 2005 WL 1398507, at *4 (D.N.J. June 10, 2005) (prior art must yield the claimed method).

There is no "irresolvable conflict" or "contradictory standards" between UTC's infringement and inherency positions. *See* Liq. Br. at 33-34. Dr. Nathan testified that it is more likely than not Yutrepia will infringe because Liquidia relied on INCREASE and told the FDA that Yutrepia would perform equally or better than Tyvaso in the INCREASE study. Tr. 95:19-96:25, 117:17-19; PTX-0377.00003-04. It simply does not follow that any administration of Tyvaso at *different* doses in a *different* patient population, as in the 2017 Study Description, would necessarily and inevitably improve exercise capacity. PFF 74-76. Indeed, Dr. Nathan testified that even in INCREASE, "it wasn't necessary and inevitable" that patients improved their exercise capacity "because there were some [patients] that didn't." Tr. 825:2-6; PFF 74-76; *see also* Tr. 541:11-14 (Channick) ("I don't know that you'd get exactly the same results."). Dr. Channick

agreed that his inherency opinion rested on probabilities, admitting that even if INCREASE were repeated and achieved a positive outcome with a p-value of 0.05, "there's still a 5 percent chance" that "the difference is by chance." Tr. 537:24-540:21. But "[i]nherency … may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Par Pharm., Inc. v. TWI Pharms.*, Inc., 773 F.3d 1186, 1195-96 (Fed. Cir. 2014); *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381-82 (Fed. Cir. 2018). None of the treatment effects of claims 1, 5, 6, 9, and 17 would "'necessarily result' from practicing" the 2017 Study Description. *Galderma*, 799 F. App'x at 845; PFF 76.

B. Liquidia's argument is premised upon the wrong legal standard

Consistent with the necessary and inevitable standard, to prevail Liquidia must demonstrate that "'virtually all' patients who take treprostinil experience an improvement in exercise capacity." D.I. 96 at 11-12; *see also Glaxo*, 2005 WL 1398507, at *4 ("[T]his teaching would only invalidate … if *virtually all* the designated recipients … also suffered from nausea, in which case the administration of ondansetron demonstrated by COATES would necessarily result in the outcome claimed[.]" (emphasis added)). Liquidia failed to meet that burden and its attempt to distinguish *Glaxo* (Liq. Br. at 31) falls flat. In *Glaxo*, inherency failed because not "virtually all" patients treated under the prior art procedure, "COATES," could experience the claimed benefit of "relief from nausea and vomiting" because it was never shown that those patients experienced nausea as a symptom. *Glaxo*, 2005 WL 1398507, at *4. *Glaxo*'s reference to "virtually all" thus must have been tied to the benefit associated with receiving the prior art treatment. Indeed, Liquidia's expert, Dr. Channick, admitted at trial that he would "almost guarantee" or could say with "confidence" that virtually all patients *would not* achieve any of the claimed treatment effects had patients taken treprostinil pursuant to the 2017 Study Description. PFF 76.

Liquidia nevertheless contends that it need only show necessary and inevitable outcomes

"in at least *one* patient in the claimed PH-ILD population." Liq. Br. at 29 (emphasis added). This makes no sense. In Liquidia's view, any claimed benefit—no matter how unlikely—would be inherent so long as "one patient" would experience it. This contradicts established inherency standards and is unsupported by *King Pharms.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010). *King Pharms.* at most stands for the principle that where a prior art method and a claimed method are *identical*, the prior art method is assumed to be as effective as the claimed method and may anticipate. 616 F.3d at 1276 ("[T]o the extent [the claimed] method increases the bioavailability of metaxalone, the *identical* prior art method does as well.") (emphasis added). There, the claimed clinical outcome—increasing bioavailability of metaxalone by administering with food—was shown to necessarily result from the prior art method of administering metaxalone with food to decrease nausea based on studies disclosed in the patent's specification. *King Pharms., Inc. v. Eon Labs, Inc.*, 593 F. Supp. 2d 501, 506, 509 (E.D.N.Y. 2009). The claimed method and the prior art method were identical, the patent "d[id] not identify any additional conditions that must be present for the food effect to occur," and the clinical studies were "assum[ed] … [to be] representative of the food effect of metaxalone on the general population," such that the results of the studies could be used to show inherent anticipation by the prior art method. *Id.* at 507-09. Likewise, in Liquidia's other case, *Montgomery*, the record made clear that the prior art was "identical to the patent itself." 677 F.3d 1375, 1382-83 & n.12 (Fed. Cir. 2012).

That is not the case here. The 2017 Study Description is *not* identical to the claimed method or INCREASE (*supra* §VIII.A). Liquidia cannot ignore these differences and sidestep its burden of establishing that the prior art achieves "the same results as the patent" by pointing to a single hypothetical patient. *Cf. King Pharms.*, 616 F.3d at 1276; *Montgomery*, 677 F.3d at 1382-83.

Liquidia's "at least one patient" argument also misses the point. The claims are directed to methods of treatment with certain outcomes, some being statistically significant. One hypothetical

patient cannot prove that the asserted prior art *methods* would have provided the claimed results. Liquidia must prove that each claimed measure would *necessarily and inevitably* have happened, but has no such evidence. PFF 71; *Salix*, 2022 WL 3225381, at *6.

The flawed "at least one patient" standard is nearly identical to the appellants' losing argument in *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 961 (Fed. Cir. 2014). There, the Federal Circuit affirmed no inherent anticipation of a claim directed to administering a compound "to a mammal" because it was "at least possible" to follow the prior art method of administering the compound to the eye without practicing the claimed method. *Id.* at 960-61 (rejecting appellants' argument that "the district court erroneously required certainty as a prerequisite for inherent anticipation."). Notably, the claim in *Allergan* recited "a" mammal, just like the claims here recite "a" patient. That was also the case in *Glaxo v. Kali Labs.*, where the claims recited administering an "effective amount" (like claim 1) to "a human" (i.e., "a patient" in claim 1) for the purpose in the preamble (like here). There was no express construction of "a," so the plain an ordinary meaning would have applied—which means the court would have used the same construction as the Court adopted here. D.I. 155. As in *Allergan*, the *Glaxo* court found no inherent anticipation. These cases foreclose Liquidia's improperly lenient standard for meeting its burden to prove inherent anticipation.

IX. CLAIM 9 IS SUPPORTED BY ADEQUATE WRITTEN DESCRIPTION

Liquidia asserts that the "statistically significant improve[ment] of [FVC]" limitation in claim 9 lacks written description support. Liq. Br. at 34-37. Liquidia's arguments fail because they overlook disclosure and misapply the law.

A. The specification describes statistically significant improvements in FVC

The '327 patent discloses FVC data demonstrating possession of the invention of claim 9. For written description, the relevant question is what the POSA would understand from the

disclosure "as a whole." *Allergan USA, Inc. v. MSN Labs. Priv. Ltd.*, 111 F.4th 1358, 1375 (Fed. Cir. 2024). The POSA reads this disclosure in view of their existing knowledge of the art. *See Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019). The specification does not need to disclose "every conceivable and future embodiment of his invention" in the specification. *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). "Representative" data and examples are enough. *Janssen Pharms., Inc. v. Tolmar, Inc.*, 718 F. Supp. 3d 394, 432 (D. Del. 2024). Liquidia ignores this law.

The '327 patent defines FVC and discloses data on the claimed improvements. FVC is "*the amount of air* that can be forcibly exhaled from the lungs after taking the deepest breath possible, as measured by spirometry." PFF 77, 80 (emphasis added). This "amount of air," or FVC, can be expressed in two different forms: "absolute" FVC is the raw volume of exhaled air (e.g., in mL or L) and "percent predicted" FVC is a normalized expression that accounts for patient variables affecting lung volume (e.g., age, sex, height, weight). PFF 78. Percent predicted FVC is more helpful clinically because it accounts for those variables. PFF 79.[7]

The specification expressly describes the invention as providing "an improvement which may be statistically significant, in forced vital capacity[.]" PFF 86. It describes measuring FVC after "at least 8 weeks," "at least 12 weeks," and "at least 16 weeks" of administering the inhaled treprostinil and includes examples of changes to both absolute FVC (e.g., "at least 20 ml") and to percent predicted FVC (e.g. "an FVC value within 5%, 10% or 20% within the FVC value prior to the administering"). PFF 86. This is not mere *ipsis verbis* disclosure (*cf.* Liq. Br. 37), this is the inventors' description of the invention in both absolute and percent predicted terms.

The specification also provides exemplary INCREASE trial data showing that the inventors

[7] Liquidia misquotes Dr. Nathan as expressing a general preference for absolute FVC. Liq. Br. at 35. His testimony specifically referred to UTC's ongoing TETON trials, which are not part of the '327 patent and study a different patient population (ILD patients without PH). PFF 79.

possessed the methods of claim 9. Table 1 describes such improvements in percent predicted FVC for the full patient population (or "ITT") receiving active treatment at 8 and 16 weeks, and the POSA would further understand this data to disclose a statistically significant improvement after 12 weeks. PFF 82. Table 1 also shows improvements in absolute FVC for the full patient population receiving active treatment at all time points. PFF 83. Tables 2-3 show statistically significant improvements for the IIP (45% of the study population) and IPF (30% of the study population) subpopulations at 16 weeks for the absolute expression of FVC. PFF 83. Further, the POSA would understand the IIP and IPF subgroup results to be predictive of patients with connective tissue disease, an additional 20% of the study population. PFF 85. And the PH-IPF results are particularly important as the data surprisingly shows benefit in the sickest PH-ILD patients. PFF 84; JTX-0001.00024 (2:37-40) (FVC usually decreases over time); PFF 86. Taken "as a whole" as the law requires, the statistically significant improvements in percent predicted FVC, statistically significant improvements in absolute FVC, and the directional improvements in absolute FVC demonstrate the inventors' possession of the invention of claim 9 (especially where Liquidia agreed at the pretrial conference that the claim includes either expression). PFF 81-86; PTC Tr. 28:24-29:5; *see also Janssen Pharms.*, 718 F. Supp. 3d at 432; *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009).

B. Liquidia's arguments fail

Seeking to manufacture a fault in the '327 patent's plainly sufficient disclosure, Liquidia misapplies the law. Liquidia repeatedly invokes legal authority specific to genus claiming to expand what is purportedly necessary to support the "full scope" of claim 9. Liq. Br. at 34, 36, 37. As described above, however, the "FVC" limitation of claim 9 is a single breath measurement with two expressions that can be converted back and forth, not a genus of species. PFF 80.

Liquidia's cases do not govern here. In *Ariad*, the specification merely "hypothesize[d]

three classes of molecules potentially capable" of the claimed result but contained "no working or even prophetic examples of methods" that could reach it. *Ariad Pharms. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355-58 (Fed. Cir. 2010) (en banc). *Juno* involved claims to "millions of billions" of antibody fragments that were (un)supported by a specification containing just two scant examples without instruction on which would bind as claimed. *Juno Therapeutics v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336-40 (Fed. Cir. 2021). The problem in *Nuvo* was not whether the inventor possessed the invention's *full scope* but the fact that there was "nothing in the specification" "showing that the inventor *actually invented* the invention claimed." *Nuvo Pharms. v. Dr. Reddy's Labs.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019). By contrast, here, there is ample evidence that the inventors actually invented the method of improving FVC, including data for both expressions of FVC in the specification. PFF 81-86. Lastly, in *Biogen*, the dispute was whether the inventors actually possessed the claimed invention when they filed an underlying provisional where the provisional was filed before the patentee learned that the specific dose (later claimed) was actually effective—unsurprisingly, there was inadequate disclosure to support the claim to that dose. *Biogen Int'l GmbH v. Mylan Pharms.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021). These cases do not apply to claim 9 here and, in any event, stand in contrast to the '327 patent's fulsome disclosure.

Liquidia is further incorrect that claim 10 compels its reading of claim 9. The POSA would not read in a requirement that the 20 ml improvement be "statistically significant" Just because claim 10 depends from 9. Instead, claim 10 can be satisfied if, for example, there was a statistically significant improvement in percent predicted FVC (as required by claim 9) as well as a *non-statistically-significant* 20 ml improvement in absolute FVC (as required by claim 10). Indeed, this exact scenario is reported in the specification for the ITT population of the INCREASE study. JTX-0001.00035 (Table 1); PFF 82, 83. Liquidia's claim 10 argument both conjures a requirement the claim does not recite and would impermissibly read out a preferred embodiment. *Vitronics*

Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996). Finally, Liquidia's reliance on *Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376 (Fed. Cir. 2022), is misplaced. Liq. Br. at 35. *Littelfuse* concerned a claim construction that "would not merely render the dependent claims superfluous, but would mean that those claims would have no scope at all." *Id*. at 1380. No such construction exists here.

Lastly, even if statistically significant improvements in both percent predicted *and* absolute FVC were necessary, the POSA would still conclude that the inventors possessed the claim. A patentee need not describe and/or enable clearly inoperable embodiments. *E.g.*, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir. 2023) ("A subset of unresponsive patients is not analogous to unsupported species in a generic claim to chemical compounds."). Here, if Liquidia contends that data is required for both expressions of FVC, the POSA could clearly identify from the patent's data which populations and time points showed statistically significant improvements in both FVC expressions. PFF 87. The POSA would also be able to identify whether and to what extent these results might be applicable to other subpopulations studied in INCREASE that were not specifically identified in the exemplary FVC data. PFF 85. Thus, the POSA would understand which expressions of FVC were operable and which were "inoperable" under Liquidia's argument. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("Even if some of the claimed combinations in a patent's scope are inoperative, the claims are not necessarily invalid. It is not a function of the claims to specifically exclude possible inoperative substances.") (cleaned up). This is not an instance where the patentee is "leaving it to the pharmaceutical industry to complete an unfinished invention." *Ariad Pharms.*, 598 F.3d 1353. Thus, even if the Court adopts Liquidia's read of claim 9, § 112 is still satisfied.

X. UTC IS ENTITLED TO STATUTORY RELIEF

Liquidia argues—for the first time—that "any proposed relief for UTC under 21 [*sic*] U.S.C. § 271(e)(4)(A) or (B) may not, as a matter of law, impact or otherwise restrict the approval and commercial marketing of Yutrepia for PAH." Liq. Br. at 37. Liquidia is incorrect. UTC is entitled to injunctive relief under both 35 U.S.C. §§ 271(e)(4)(A) and 271(e)(4)(B). The injunction required by § 271(e)(4)(A) is *mandatory* ("shall") and must be directed to "*any approval* of the drug … involved in the infringement." 35 U.S.C. § 271(e)(4)(A) (emphasis added).

XI. CONCLUSION

Liquidia has not proven by clear and convincing evidence that any asserted claim is invalid. UTC therefore respectfully requests that the Court enter judgment that the claims are not invalid.

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July 24, 2025

CERTIFICATE OF SERVICE

I hereby certify that on July 24, 2025, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on July 24, 2025, upon the following in the manner indicated:

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